Aspekte der Beeinflussung chronischen Rückenschmerzes durch zentralnervöse Prozesse

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Zusammenfassung

Die meisten Menschen westlicher Länder leiden im Lauf ihres Lebens zumindest zeitweise unter Rückenschmerzen. In der Mehrzahl der Fälle verschwinden die Schmerzen von alleine wieder, bei einigen bleiben sie jedoch – oftmals ohne erkennbaren somatischen Pathomechanismus – bestehen. Seit Jahren häufen sich wissenschaftliche Veröffentlichungen, die eine Beteiligung kognitiver Prozesse bei der Entstehung und Aufrechterhaltung von chronischem Rückenschmerz nahelegen. Ziel dieser Arbeit ist es, einzelne kognitive Einflussvariablen auf Aktivierungen in Strukturen des Großhirns sowie Möglichkeiten einer differenziellen Aktivierung relevanter Hirnstammstrukturen zu untersuchen, die bei der Verarbeitung und Modulation von chronischem Rückenschmerz zum Tragen kommen. Als Untersuchungsmethode wird die funktionelle Magnetresonanztomographie (fMRT) eingesetzt. Die Arbeit fasst 3 Manuskripte zusammen, von denen zwei bereits publiziert sind und eines, das bei einer Fachzeitschrift eingereicht wurde und sich in Überarbeitung befindet.

Studie 1 untersucht kortikale Mechanismen, die für die Diskrimination von Gewichtsunterschieden eine Rolle spielen. Eine vorangegangene Studie hatte ergeben, dass diese Diskriminationsleistung bei chronischen Rückenschmerzpatienten beeinträchtigt ist, wenn der Rücken in den Gewichtstransfer einbezogen war. Bei gesunden Kontrollpersonen wurden für die Bearbeitung dieser Diskriminationsaufgabe eine deutliche Somatotopie im somatosensorischen Kortex sowie Aktivierungen unter anderem im anterioren zingulären Kortex und der Insula gefunden. Diese Ergebnisse liefern wichtige Hinweise, weshalb chronischer Rückenschmerz die Bewältigung der Gewichtsdiskrimination beeinträchtigen könnte.

Studie 2 hatte zum Ziel, eine Methode zur differentiellen Aktivierung von Hirnstamm-Strukturen zu finden, die auf die absteigende Schmerzhemmung Einfluss nehmen. Weil chronischer Rückenschmerz mit der Wahrnehmungsqualität „zweiter Schmerz“ verbunden ist, sollte das Paradigma die Möglichkeit einräumen, die Verarbeitung dieser Schmerzqualität im Hirnstamm aufzuzeigen. Die Stimulation mit verschiedenen Hitzereizen führte zu einer differentiellen Wahrnehmung der Schmerzqualität und zu einer differentiellen Aktivierung von periaquäduktalem Höhlengrau und rostraler ventromedialer Medulla. Damit ist es möglich, dieses Paradigma einzusetzen, wenn der Einfluss des „zweiten Schmerzes“ auf Aktivierung dieser Hirnstammareale untersucht werden soll.

Studie 3 hatte zum Ziel, neuronale Aktivierungen, die von schmerzassoziierten Wörtern – im Unterschied zu neutralen, negativen und positiven – verursacht werden, zwischen chronischen Rückenschmerzpatienten und gesunden Kontrollprobanden zu vergleichen. Außerdem sollte

der Einfluss des Ausmaßes aktueller, d. h. im Experiment auftretender, Schmerzen auf die Verarbeitung der verbalen Reize untersucht werden. Es zeigten sich bei chronischen Rückenschmerzpatienten höhere Aktivierungen als bei gesunden Kontrollprobanden beim Vergleich der Aktivierungen zwischen schmerzassoziierten und negativen Wörtern im subgenualen anterioren zigulären Kortex, im präfrontalen Kortex, im posterioren mittleren zingulären Kortex sowie bilateral in der Insula. In der Gruppe der chronischen Rückenschmerzpatienten gab es einen linearen, positiven Einfluss des aktuellen Schmerzes auf die Höhe des Aktivierungsunterschiedes im Kontrast zwischen schmerzassoziierten Wörtern und allen anderen Wortkategorien.

Die vorliegende Arbeit zeigt Möglichkeiten auf, wie mit fMRT Einflüsse kognitiver Prozesse untersucht werden können, die bei der Verarbeitung nozizeptiver und schmerzassoziierter Reize bei Gesunden sowie bei Rückenschmerzpatienten von Bedeutung sind. Studie 1 und 2 erbringen Befunde an gesunden Kontrollprobanden, sie sind Grundlage für eine weitere Hypothesenbildung und schaffen methodische Grundlagen für die Untersuchung an Rückenschmerzpatienten. Studie 3 zeigt bei dieser Patientengruppe, dass eine Wechselwirkung zwischen der Verarbeitung sprachlicher, schmerzbezogener Reize und dem Ausmaß chronischer und aktueller Rückenschmerzen besteht.

Summary

Most people in western countries suffer back pain sometime in their life. Although pain usually disappears with the healing, it may become chronic. The pathogenetic mechanisms leading to chronic back pain are still elusive. Recent evidence suggests that high-level cortical representations play a role in chronic back pain. The rationale of this thesis is that chronic back pain is influenced by higher cortical representations and the descending pain control system. These interdependencies are investigated by means of functional magnetic resonance imaging (fMRI). This thesis summarizes two studies that are already published. A third manuscript has been submitted and is currently under revision.

Study 1 investigated cortical mechanisms involved in the discrimination of different weights which are lifted with different movements. This weight discrimination was already shown to be disturbed in chronic back pain patients when the weight lifting movement involved the back. When healthy controls performed this task in the actual study, a clear somatotopy in somatosensory cortex as well as activations in anterior cingulate cortex and in the insula were found. These findings provide important information as to why chronic back pain may interfere with the weight discrimination task.

Study 2 aimed at finding a method for differentiating structures in the brain stem that are involved in descending pain control and associated with differential processing of different qualities of pain. Especially “second pain” is of crucial importance in the experience of chronic pain. Thus, its modulation would be of interest especially for chronic back pain patients. The results provide evidence that the brain stem periaqueductal grey and the rostral ventromedial medulla become differentially activated by different types of noxious skin heating. These stimuli were associated with the perception of ”first” and “second pain”. Therefore, this stimulation can be utilized when different perceptual qualities of pain are investigated and when it is aimed to activate major structures in the brain stem differentially.

Study 3 aims to compare neural activations induced by pain-related words vs. negative, neutral, and positive words between a sample of chronic back pain patients and healthy controls. In addition, the influence of current pain, i. e. pain suffered during the experimental session, in chronic back pain patients on the processing of pain related words was investigated. Higher activations were found in chronic back pain patients vs. healthy controls for pain-related vs. negative words in the subgenual anterior cingulate cortex, in the prefrontal cortex, in thepos-

terior midcingulate cortex, and bilaterally in the anterior insula. The amount of higher activation for pain-related vs. all other word categories showed a positive linear relationship to current pain.

This thesis summarizes three studies that show possible applications of fMRI to examine cognitive influences on chronic back pain, which are crucial to the processing of nociceptive input in healthy control subjects and chronic back pain patients. Study 1 and 2 report relevant results collected on healthy control subjects which may form the methodological basis for the investigation of chronic back pain patients. For this patient group, study 3 reveals a significant interaction between the processing of pain-relevant verbal cues and the actual intensity of chronic back pain.

Inhaltsverzeichnis

1 Einleitung

Im Alltag vieler Menschen sind Rückenschmerzen eine erhebliche Belastung und verursachen von allen Krankheitsbildern die höchsten Kosten im Gesundheitssystem. Die 12-Monats-Prävalenz von Rückenschmerzen beträgt in der BRD 66% bei Frauen und 58% bei Männern (Neuhauser, Ellert, & Ziese, 2005). Die Prävalenzrate chronischer Schmerzen in der BRD beträgt 32,9 % (Hauser, Schmutzer, Hinz, Hilbert, & Brahler, 2013). Unter anderem deshalb hat die WHO als eines ihrer bedeutendsten Ziele für die Zukunft die Verbesserung der Schmerzbehandlung angegeben. Voraussetzung dafür ist eine intensive Erforschung der Pathophysiologie der verschiedenen Schmerzsyndrome. Zunahme, Aufrechterhaltung und Verselbstständigung chronischer Rückenschmerzen sind bislang zu großen Teilen nicht gut verstanden und werden daher in zunehmendem Maß auch unter psychologischen Gesichtspunkten erforscht.
Chronischer Schmerz wurde seit den 1960er Jahren zunehmend als eigenständige klinische Störung wahrgenommen und nicht mehr nur als eine Folgeerscheinung von Verletzungen (Flor & Turk, 2011). Seit Melzack und Walls richtungsweisender „gate control theory“ wird Schmerz als Form bewusster sensorischer Wahrnehmung gesehen, die Resultat von zwischen Großhirn und Rückenmark ab- und aufsteigender Einflüsse ist (Melzack, 1999; Melzack & Wall, 1965). Schmerz wird als eine komplexe, integrierte Reaktion begriffen, die sensorische, emotionale, kognitive, motorische und behaviorale Komponenten beinhaltet und die auf einer physiologischen, verbal-subjektiven und motorisch-behavioralen Ebene beschrieben werden kann (Flor & Turk, 2011). Eine Einteilung in akute und chronische Schmerzen hat sich klinisch als nützlich erwiesen, wobei als zeitliches Kriterium für Chronizität meist 3 oder 6 Monate genutzt wird oder die Formulierung, dass es sich um Schmerz handele, der über die erwartete Zeit der Heilung hinaus besteht. Dabei erweist sich die Unterscheidung zwischen akutem und chronischem Schmerz als nicht einfach. Flor und Turk (2011) begreifen chronischen Schmerz als „Schmerz, der nicht gut lokalisierbar ist, trotz Gegenmaßnahmen weiter besteht, nicht immer durch organische Pathologie erklärt werden kann, die Person einschränkt und Gefühle von Hilflosigkeit, emotionalem Stress wie Depression, Ärger, Angst und Frustration auslöst. Chronischer Schmerz ist oft von Inaktivität begleitet und kann zunehmend im Alltag behindern“ (Flor & Turk, 2011).
Chronische Rückenschmerzen treten bei etwa 8 von 10 Betroffenen, als sogenannte „funktionelle“ oder „unspezifische“ Rückenschmerzen (Koes, van Tulder, & Thomas, 2006) auf, bei

denen sich die Beschwerden nicht auf ursächliche Krankheitsprozesse, wie etwa Bandscheibenvorfälle, zurückführen lassen. Als Erklärung der Beschwerden werden unter anderem Veränderungen von Mechanismen, die mit der Entstehung von chronischem Schmerz im Zentralnervensystem (ZNS) einhergehen, diskutiert (Ahern, Bishop, Follick, Gelch, Lucas, Parziale, Marras, Wilkin, & Wolf, 1990; Apkarian, Bushnell, Treede, & Zubieta, 2005; Apkarian, Sosa, Sonty, Levy, Harden, Parrish, & Gitelman, 2004; Baliki, Chialvo, Geha, Levy, Harden, Parrish, & Apkarian, 2006; Baliki, Geha, Fields, & Apkarian, 2010; Baliki, Petre, Torbey, Herrmann, Huang, Schnitzer, Fields, & Apkarian, 2012; Flor, Braun, Elbert, & Birbaumer, 1997; Harris, 1999; Lotze & Moseley, 2007; Richter, Eck, Straube, Miltner, & Weiss, 2010; Siddall, Stanwell, Woodhouse, Somorjai, Dolenko, Nikulin, Bourne, Himmelreich, Lean, Cousins, & Mountford, 2006; Wand, Parkitny, O'Connell, Luomajoki, McAuley, Thacker, & Moseley, 2011). So konnte beispielsweise gezeigt werden, dass im Zusammenhang mit chronischem Rückenschmerz die kognitive Repräsentation des Körpers verändert ist (Bray & Moseley, 2011). Dass die Grundlage für die Chronifizierung von Rückenschmerzen in kortikalen Veränderungen wie der Dicke der grauen Masse und bei Verbindungen bestimmter Areale zueinander zu suchen sein könnte, wurde kürzlich anhand von Ergebnissen aus fMRT-Studien nahegelegt (Baliki et al., 2010; Baliki et al., 2012). Es wird weiterhin vermutet, dass chronische Schmerzen mit Veränderungen bei der körpereigenen, absteigenden Schmerzhemmung einhergehen (Bingel, Schoell, & Büchel, 2007; Staud, 2011). Auch die kortikale Verarbeitung nicht-noxischer Reize, wie etwa schmerz-assoziierter Wörter, unterscheidet sich signifikant zwischen chronischen Schmerzpatienten und gesunden Kontrollprobanden (Eck, Richter, Straube, Miltner, & Weiss, 2011).

Die vorliegende Arbeit befasst sich mit Veränderungen von Verarbeitungsvorgängen im ZNS, die im Zusammenhang mit chronischem Rückenschmerz stehen. Alle Studien wurden im Rahmen des vom Bundesministerium für Bildung und Forschung geförderten Projektes „Chronic back pain and sensory-motor control: towards a model based diagnostic toolbox“ durchgeführt. Als Methode wird übergreifend funktionelle Magnetresonanztomographie (fMRT) angewendet. Studie 1 und 2 zielen darauf ab, experimentelle Paradigmen an gesunden Kontrollpersonen zu erproben. Studie 1 fragt nach neuronalen Grundlagen, die für die Diskrimination von Gewichtsunterschieden bei von Lichtpunktefiguren ausgeführten Hebebewegungen eine Rolle spielen, weil diese Leistung bei chronischen Rückenschmerzpatienten beeinträchtigt ist (de Lussanet, Behrendt, Puta, Schulte, Lappe, Weiss, Schuppe, & Wagner, 2013; de Lussanet, Behrendt, Puta, Weiss, Lappe, Schulte, & Wagner, 2012). Studie 2 testet

ein neues Paradigma, das ermöglichen soll, für die absteigende Schmerzhemmung wesentliche Strukturen im Bereich des Hirnstamms differentiell zu aktivieren, die bei chronischem Schmerz möglicherweise krankhaft verändert sind. Ein spezieller Fokus liegt dabei auf der Abgrenzung von Phänomenen des „zweiten Schmerzes“, weil diese Schmerzqualität bei chronischen Rückenschmerzen vorrangig die subjektive Schmerzwahrnehmung bestimmt. In Studie 3 wird an einer Gruppe von Patienten mit chronischem unspezifischen Rückenschmerz getestet, welche Aktivierungsunterschiede sich im Gehirn bei der Verarbeitung von schmerzassoziierten und nicht-schmerzassoziierten Wörtern ergeben. Dabei interessierte auch der Einfluss aktueller, d. h. während des Experimentes wahrgenommener Schmerzen auf die Verarbeitung des verbalen Reizmaterials.

2 Chronischer Rückenschmerz und Nervensystem

Zur Einordnung der drei vorliegenden Manuskripte sollen nachfolgend verschiedene Aspekte umrissen werden, die für das Verständnis der formulierten Untersuchungsziele notwendig sind. Die spezifischen, zu den einzelnen Fragestellungen der Studien hinleitenden Zusammenhänge werden im darauffolgenden Abschnitt dieser Arbeit aufgeführt.

2.1 Mechanismen der Schmerzverarbeitung im Zentralnervensystem

In den drei in dieser Arbeit zusammengefassten Studien haben die Mechanismen der Verarbeitung von Schmerz im Gehirn eine zentrale Bedeutung.
Schmerz als psychologischer Zustand entsteht als Ergebnis kortikaler Verarbeitung im Zentralnervensystem (ZNS) (Miltner & Weiss, 2000) und ist von den peripheren Mechanismen der Nozizeption abzugrenzen (Merskey, 1979). Neben der Verarbeitung von Information aufsteigender nozizeptiver Nervenbahnen, die diffus in verschiedene Bereiche des Kortex projizieren (Creutzfeldt, 1983), bestimmen Gedächtnisinhalte, Lernerfahrungen, emotionale und motivationale Prozesse, sowie individuelle Bewältigungsmechanismen die unangenehme sensorische und emotionale Erfahrung Schmerz.

Die nozizeptive Information gelangt über den spinothalamischen Trakt in das Gehirn. Dabei sind das „laterale“ und das „mediale System“ zu unterscheiden, die eine hinlängliche Einordnung der nachfolgenden zentralen Schmerzverarbeitung zulassen (Magerl & Treede, 2011).
Die sensorisch-diskriminative Dimension des Schmerzes wird vorwiegend über das „laterale System“ verarbeitet: von lateralen Thalamuskernen ziehen Bahnen zum primären und sekundären somatosensorischen Kortex (S1 und S2) sowie zum posterioren parietalen Kortex. Dieses Subsystem ist an der Verarbeitung von Intensität, Größe und Ort der Noxe beteiligt. Es konnte bei chronischen Rückenschmerzpatienten bereits gezeigt werden, dass S1 im Unterschied zu gesunden Kontrollprobanden in seinem superioren Anteil, welcher unter anderem den Bereich des Rückens somatotop repräsentiert, eine höhere kortikale Dicke aufweist (Kong, Spaeth, Wey, Cheetham, Cook, Jensen, Tan, Liu, Wang, Loggia, Napadow, Smoller,

Wasan, & Gollub, 2013). Diese Zunahme an kortikalem Volumen in S1 könnte als Hinweis dafür gesehen werden, dass die Sensitivität für Schmerz steigt (Davis & Moayedi, 2013).
Die affektiv-motivationale Dimension des Schmerzes, die beim „zweiten Schmerz" und damit auch besonders bei chronischen Schmerzen zum Tragen kommt, wird vorwiegend über das „mediale System" verarbeitet: mediale Thalamuskerne innervieren unter anderem die Insula, den anterioren zingulären Kortex sowie den präfrontalen Kortex. Baliki et al. konnten zeigen, dass mehr als 70 % der Varianz der Dauer des chronischen Rückenschmerzes mit einer Aktivierung der Insula sowie 80% der Varianz der Intensität des chronischen Rückenschmerzes mit einer Aktivierung des medialen Präfrontalkortex erklärt werden können (2006).
Neben der Verarbeitung der sensorisch-diskriminativen und der affektiv-motivationalen Dimension des Schmerzes werden auch schmerzbezogene allgemeine Aktivierungsvorgänge und hormonelle Prozesse von Strukturen des ZNS initiiert. Sie gehen von subkortikalen Arealen wie dem Hirnstamm und dem Hypothalamus aus. Diese Areale sind wiederum mit kortikalen Arealen assoziiert (Apkarian, Bushnell, Treede, & Zubieta, 2005). Für chronischen Rückenschmerz konnte gezeigt werden, dass das Ausmaß der funktionellen Konnektivität (Friston, 2011) zwischen dem subkortikalen Nucleus accumbens und dem medialen Präforntalkortex ein Prädiktor für den Übergang von subakutem zu chronischem Rückenschmerz ist (Baliki et al., 2012).

Generell sind die der Schmerzverarbeitung zugrundeliegenden kortikalen Prozesse stark von psychologischen Einflussgrößen wie Lernen (Miltner, Braun, Arnold, Witte, & Taub, 1999; Weiss, Miltner, & Dillmann, 2003), Erwartungshaltungen (Koyama, McHaffie, Laurienti, & Coghill, 2005; Wager, Rilling, Smith, Sokolik, Casey, Davidson, Kosslyn, Rose, & Cohen, 2004), emotionalen Zuständen (Decety, Jackson, Brunet, & Meltzoff, 2006; Godinho, Magnin, Frot, Perchet, & Garcia-Larrea, 2006; Kenntner-Mabiala & Pauli, 2005; Loggia, Mogil, & Bushnell, 2008; Rainville, Bao, & Chretien, 2005; Singer, Seymour, O'Doherty, Kaube, Dolan, & Frith, 2004) und Aufmerksamkeit (Davis & Seminowicz, 2007; Friederich, Trippe, Ozcan, Weiss, Hecht, & Miltner, 2001; Kenntner-Mabiala, Weyers, & Pauli, 2007; Miltner, Johnson, Braun, & Larbig, 1989; Valet, Sprenger, Boecker, Willoch, Rummeny, Conrad, Erhard, & Tolle, 2004; Villemure, Slotnick, & Bushnell, 2003) abhängig. Die unter anderem für die Schmerzverarbeitung wesentlichen Hirnstrukturen und Netzwerke (Iannetti, Hughes, Lee, & Mouraux, 2008; Iannetti & Mouraux, 2010; Legrain, Iannetti, Plaghki, & Mouraux, 2011) können so auch etwa durch semantische und visuelle schmerzassoziierte Reize aktiviert werden, die für die betreffende Person eine hohe Salienz aufweisen.

Dieses Prinzip bildet die Grundlage für Studie 3 und ist auch für Studie 1 relevant. So bilden sich zur Verarbeitung der nozizeptiven Information verteilte Nervenzellensembles zwischen Thalamus und Neokortex sowie im limbischen System. Wiederholte zyklische Verarbeitung und Synthese der Nervenimpulse dieser Ensembles ergeben ein charakteristisches Muster. Dieses Muster kann konzeptuell als Hebb´scher Zellverband (Hebb, 1949) gefasst werden, dessen neural-synaptische Struktur genetisch angelegt ist und in welchem synaptischer Wettbewerb zu Neuentstehung und Auflösung von Synapsen führt, so dass letztlich die für den Körper einzigartige neural-synaptische Architektur entsteht. Die auf diese Weise stattfindenden Lernvorgänge könnten die individuellen Unterschieden beim Erleben (chronischer) Schmerzen erklären (Katz & Melzack, 1990): Wenn es zu einer noxischen Reizung kommt, werden simultan emotionale und semantische Repräsentationen aktiviert, weshalb die Stärke der Assoziation des entsprechenden neuronalen Substrates zunimmt und wodurch die Schmerzerfahrung immer wieder emotional und semantisch überformt und neu gestaltet wird (Bower, 1981). Auf diese Weise können beispielsweise schmerzbeschreibende verbale Stimuli, wie die in Studie 3 verwendeten, die Schmerzempfindung beeinflussen (Dutt-Gupta, Bown, & Cyna, 2007; Ott, Aust, Nouri, & Promberger, 2012) und entsprechende schmerzverarbeitende Hirnstrukturen aktivieren (Eck et al., 2011; Gu & Han, 2007; Osaka, Osaka, Morishita, Kondo, & Fukuyama, 2004; Richter et al., 2010).

2.2 Präferentielle Erfassung von erstem und zweitem Schmerz

Für Studie 2 war es wesentlich, die beiden Klassen schmerzleitender Nervenfasern unabhängig voneinander zu stimulieren und die damit einhergehende Qualität der Schmerzwahrnehmung zu erfassen.

Nozizeption resultiert aus den sensorischen Eingängen zweier verschiedener peripherer Nervenfasern, deren Information im ZNS teilweise unterschiedlich verarbeitet wird und die zu unterschiedlichen Qualitäten der Schmerzempfindung beitragen: Die gering myelinisierten Aδ-Fasern transferieren den „ersten Schmerz“ von den Nozizeptoren der Peripherie zum ZNS, während die weitaus langsamer leitenden, nicht myelinisierten C-Fasern den „zweiten Schmerz“ übertragen. Mit „erstem Schmerz“ ist das sofort nach einer Verletzung auftretende, gut lokalisierbare und schnell abklingende Schmerzempfinden gemeint, während der „zweite Schmerz“ eine dumpfe, schlecht lokalisierbare und wesentlich länger anhaltende Qualität der Schmerzwahrnehmung bezeichnet, die für chronische Schmerzerkrankungen die wesentliche Form der Symptomatik darstellt. Die zentralnervöse Verarbeitung der Impulse aus Aδ- und

C-Fasern erfolgt trotz Überlappungen in unterschiedlichen kortikalen und subkortikalen Systemen (Forss, Raij, Seppa, & Hari, 2005; Ploner, Gross, Timmermann, & Schnitzler, 2002; Price, 2000; Price & McHaffie, 1988; Qiu, Noguchi, Honda, Nakata, Tamura, Tanaka, Sadato, Wang, Inui, & Kakigi, 2006; Weiss, 2008; T. Weiss, T. Straube, J. Boettcher, H. Hecht, D. Spohn, & Miltner, 2008). So ergab die Reizung von C-Fasern im Vergleich zur Stimulation von Aδ-Fasern zusätzliche Aktivierungen des frontalen Operculums, des inferioren frontalen Kortex und der anterioren Insula (Weiss, 2008). Die Autoren dieser Studie schlussfolgerten, dass die Verarbeitung der Information des C-Faser-Systems neben somatosensorischen und nozizeptiven Anteilen auch homöostatische und interozeptive Funktionen hat. Insgesamt lässt sich aus den genannten Studien erschließen, dass der „erste Schmerz" das Individuum über den Ort der Verletzung sowie dessen sensorische Qualität informiert, wohingegen der „zweite Schmerz" für die fortdauernde Ausrichtung der Aufmerksamkeit des Individuums auf die Verletzung, den schmerzbezogenen Affekt sowie für „coping"-Mechanismen, also die Einleitung von günstigen Verhaltensweisen zur optimalen Heilung, verantwortlich ist (Ploner et al., 2002; Price, 2000; Price & McHaffie, 1988; Qiu et al., 2006; Weiss et al., 2008). So tragen Aδ- und C-Faser-System auch auf unterschiedliche Weise zu diversen Schmerzsymptomen bei. Eine selektive Stimulation der beiden Fasersysteme ist daher bedeutsam für die Schmerzforschung und die klinische Praxis. Allerdings erweist sich die systematische und differenzierte Untersuchung von Aδ- und C-Fasern als kompliziert. Sensitive Verfahren wie die Mikroneurographie zur Charakterisierung der stimulierten Faser (Handwerker, 1996; Schmelz, Forster, Schmidt, Ringkamp, Handwerker, & Torebjork, 1995) und die Methode der Stimulation winziger Hautareale (Bragard, Chen, & Plaghki, 1996) zur selektiven Reizung der Fasern können aufgrund ihres hohen Aufwandes oft nicht im klinischen Alltag durchgeführt werden. Deshalb stellt die Suche nach geeigneten Alternativen eine herausfordernde Forschungsaufgabe dar.

Die selektive Reizung von C-Fasern kann neben der Methode der Stimulation winziger Hautareale mit Laserhitzereizen (Bragard et al., 1996) unter anderem auch mit der flächigen Applikation von Hitze mit unterschiedlich schnellem Temperaturanstieg unternommen werden (Lumb, 2002; Lumb, Parry, Semenenko, McMullan, & Simpson, 2002; Price, Hu, Dubner, & Gracely, 1977; Staud, Craggs, Robinson, Perlstein, & Price, 2007; Yarnitsky, Simone, Dotson, Cline, & Ochoa, 1992; Yeomans & Proudfit, 1996). Einen zugrunde liegenden Mechanismus dafür stellt das „wind up"-Phänomen (Mendell & Wall, 1965) dar. Entscheidend für dessen Auftreten sind die bei aufeinanderfolgenden Hitzereizen zwischen den Spitzentemperaturen liegenden Phasen der Reizung, in denen die applizierte Temperatur

unter die Schwelle von ca. 43°C fällt, bei der schmerzleitende C-Fasern nicht mehr aktiviert werden (Julius & Basbaum, 2001). Bei wiederholter und überschwelliger thermischer (oder mechanischer) Reizung mit einer Stimulationsfrequenz von $f \geq 0{,}3$ Hz kommt es zu einer Erhöhung der Aktionspotential-Frequenz innerhalb einer C-Faser im dorsalen Horn des Rückenmarks. Bei einem einzelnen adäquaten Reiz bewirkt das von der C-Faser ankommende Aktionspotential eine Freisetzung des Neurotransmitters Glutamat in den synaptischen Spalt. Dieser bindet an die Glutamatrezeptoren des AMPA-Subtyps GluR1-4 der Postsynapse, öffnet diese und erzeugt so über Natrium- und Calciumeinstrom ein schnelles exzitatorisches postsynaptisches Potential im Neuron des dorsalen Horns. In Folge einer wiederholten C-Faser-Stimulation und einer damit einhergehenden erhöhten Calcium-Konzentration in der Präsynapse erfolgt eine zusätzliche Ausschüttung verschiedener Transmitter wie zum Beispiel Substanz P, die über den G-Protein-gekoppelten Neurokinin-Rezeptor ein zusätzliches langsames exzitatorisches postsynaptisches Potential auslösen (Fields, Rowbotham, & Baron, 1998; Mendell, 1984; Mendell & Wall, 1965). Für Studie 2 ist vor allem von Bedeutung, dass es sich beim „wind up"-Phänomen um einen von C-Fasern vermittelten Prozess handelt. Dies könnte erklären, weshalb die Hitzestimulation in einer der Bedingungen mit Begriffen des „zweiten Schmerzes" beschrieben wurde.

Eine günstige Variante, eine Stimulation auf Anteile des „ersten" und des „zweiten Schmerzes" zu untersuchen, stellt ein Kurzfragebogen mit drei verbalen Schmerz-Deskriptoren (Beissner, Brandau, Henke, Felden, Baumgartner, Treede, Oertel, & Lotsch, 2010) dar, der auch in Studei 2 zum Einsatz kommt. Die drei Schmerzdeskriptoren „piksend" (Aδ-Faser), „drückend" und „dumpf" (C-Faser) diskriminieren mit einer Spezifität von 95% zwischen den Qualitäten „erster Schmerz" und „zweiter Schmerz", die von Aδ- bzw. von C-Fasern vermittelt werden.

2.3 Absteigendes Schmerzhemmsystem

Das nozizeptive System verfügt nicht nur über aufsteigende Nervenbahnen, die die Information von der Peripherie an das Gehirn weiterleiten. Es enthält auch organisierende Mechanismen im ZNS, die den nozizeptiven Input „absteigend hemmen". Sind diese Hemmsysteme beeinträchtigt, beeinflusst dies die Entstehung der Symptome chronischen Schmerzes (Bingel, 2007; Staud, 2011). Eine experimentelle Modulation der Aktivität in Strukturen des absteigenden Schmerzhemmsystems steht im Fokus von Studie 2.

Seit Basbaum und Fields 1984 zeigen konnten, dass sich durch elektrische Stimulation im periaquäduktalen Höhlengrau (PAG) des Hirnstamms eine profunde Analgesie erreichen lässt, gilt diese Struktur als Ausgangspunkt der absteigenden Schmerzhemmung (1984). Im PAG sind zahlreiche endorphinerge Neurone zu finden, die von hier aus und vom benachbarten serotonergen Nucleus Raphe dorsalis (NRD) zum Nucleus Raphe magnus (NRM), einem Teil der rostralen ventromedialen Medulla (RVM), deszendieren. Nach der Passage des Hirnstamms ziehen diese Faserverbände zum dorsolateralen Funiculus des Rückenmarks, wo sie über Interneurone eine tonische Hemmung in Nervenzellen des Rückenmarks bewirken. Angeregt wird diese Kaskade durch kortikale und subkortikale Strukturen: An Initiation und Aufrechterhaltung der absteigenden Schmerzhemmung sind wesentlich der dorsolaterale präfrontale Kortex und der rostrale anteriore zinguläre Kortex beteiligt (Bingel, 2007). Weil diese kognitiven Leistungen bei der Schmerzverarbeitung durch Formung und Abruf von Gedächtnisinhalten, aber auch durch Stress, Katastrophisieren, Angst, Depression, Lernerfahrung und Priming beeinflussbar sind, bietet sich hier ein Ansatzpunkt zur Manipulation des chronischen Schmerzes mit psychologischen Variablen und psychotherapeutischen Interventionen.

2.4 Chronischer Rückenschmerz und Bewegung

Eine starke Wechselwirkung besteht zwischen chronischem Rückenschmerz und dem motorischen System. Diese gegenseitige Einflussnahme bildet die Grundlage für die in Studie 1 formulierten Hypothesen.

Auf das akute Auftreten chronischer Rückenschmerzen folgt eine motorische Reaktion, die die Stütz- und Zielmotorik gleichermaßen betrifft: neben dem Einnehmen einer Schonhaltung und einer allgemeinen Verlangsamung von Bewegungen ist auch eine Änderung von Bewegungsabläufen feststellbar (Ahern et al., 1990; Basler, Luckmann, Wolf, & Quint, 2008; Sternbach, Wolf, Murphy, & Akeson, 1973). So kann chronischer Schmerz zu Veränderungen der sensomotorischen Repräsentation in den primären motorischen und sensorischen Kortizes führen, wodurch sich das Körperschema der Patienten verändern kann (Lauche, Cramer, Haller, Musial, Langhorst, Dobos, & Berger, 2012; Moseley, 2008). Bei chronischem Rückenschmerz konnte eine schlechtere Leistung bei der Zweipunktdiskrimination (Luomajoki & Moseley, 2011) sowie bei der Aufgabe, Angaben über die räumliche Ausdehnung des von chronischen Schmerzen betroffenen Areals zu zeichnen (Moseley, 2008), festgestellt werden. Darüber hinaus kann die bloße Vorstellung von bestimmten Haltungen oder Bewegungen Schmerzen bei Patienten auslösen, sobald die von chronischen Schmerzen betroffene Körperregion Teil der vorgestellten Haltung oder Bewegung ist (Moseley, Zalucki, Birklein, Marinus, van Hilten, & Luomajoki, 2008). Eine kortikale Beteiligung bei diesen Vorgängen kommt prominent dem somatosensorischen und dem motorischen Kortex zu, vor allem, wenn bei den Bewegungen Werkzeuge oder Gegenstände manipuliert werden (Fogassi & Luppino, 2005; Pineda, 2008; Rizzolatti & Fabbri-Destro, 2010; Sacco, Cauda, Cerliani, Mate, Duca, & Geminiani, 2006).

Eine Möglichkeit zur Untersuchung von beobachteten Bewegungen bietet die Technik der animierten Lichtpunktefiguren, wie sie in Studie 1 zur Anwendung kommt. Hierbei handelt es sich um eine stark reduzierte visuelle Darstellung menschlicher Bewegung durch mit Lichtpunkten markierte Stellen am Körpers (Johansson, 1973). Von den Bewegungen dieser abstrakten Figuren können Betrachter auf verschiedene Merkmale wie Geschlecht (Pollick, Kay, Heim, & Stringer, 2005), Richtung der Bewegung (Hirashima, 1999) oder die Emotionen der handelnden „Personen“ (Alaerts, Nackaerts, Meyns, Swinnen, & Wenderoth, 2011) schließen.

Es gelingt Beobachten ebenfalls, das Gewicht eines Objektes, das von Lichtpunktefiguren gehoben oder transportiert wird, zu bestimmen (Runeson & Frykholm, 1981). Diese Gewichts-Schätzaufgabe ist besonders für die Untersuchung der Verbindung des visuellen mit dem sensomotorischen Systems geeignet (Alaerts, Swinnen, & Wenderoth, 2010; Auvray, Hoellinger, Hanneton, & Roby-Brami, 2011; Bingham, 1987; Bosbach, Cole, Prinz, & Knoblich, 2005; de Lussanet et al., 2012; Hamilton, Wolpert, & Frith, 2004; Marquez, Ceux, & Wenderoth, 2011; Poliakoff, Galpin, Dick, & Tipper, 2010; Shim, Ringkamp, Lambrinos, Hartke, Griffin, & Meyer, 2007). Mit dieser Aufgabe ergibt sich eine Möglichkeit, die bei chronischem Rückenschmerz auftretenden sensorischen und motorischen Anomalien zu untersuchen.

3 Einordung der Manuskripte

Manuskript 1: „Brain activity for visual judgment of lifted weight"

Chronische Rückenschmerzpatienten unterscheiden sich in ihren Reaktionen auf ein weites Spektrum von Reizen, auch auf solche, die nur mittelbar mit ihrem schmerzspezifischen Erleben assoziiert sind. So sind im Zuge von chronischen Schmerzerkrankungen Bewegung und Bewegungswahrnehmung stark beeinträchtigt (de Lussanet et al., 2013; de Lussanet et al., 2012). Daneben ändern sich auch relevante Bewegungsabläufe (Hodges & Tucker, 2011) bei den Patienten. De Lussanet et al. konnten kürzlich nachweisen, dass bei einer Gewichts-Schätzaufgabe signifikante Unterschiede zwischen chronischen Rücken- und Schulterschmerzpatienten sowie zu gesunden Kontrollprobanden bestehen (de Lussanet et al., 2013; de Lussanet et al., 2012). Chronische Rückenschmerzpatienten konnten das gehobene Gewicht schlechter als gesunde Kontrollprobanden schätzen, wenn die Bewegung wesentlich im unteren Rückenbereich stattfand, während chronische Schulterschmerzpatienten das gehobene Gewicht schlechter als gesunde Kontrollprobanden schätzten, wenn die Bewegung hauptsächlich im Schulterbereich stattfand (de Lussanet et al., 2013). Diese Ergebnisse verdeutlichen, dass es eine grundlegende Wechselwirkung zwischen chronischem Schmerzempfinden und der Beurteilung von Handlungen anderer gibt. Dies lässt die Hypothese zu, dass chronischer Schmerz jene Hirnregionen beeinflusst, die mit der Beurteilung von Aspekten der Bewegung von Lichtpunktefiguren in Verbindung stehen. Das Ziel dieser Studie war, im fMRT bei gesunden Kontrollprobanden jene Gehirnregionen zu identifizieren, die aktiv sind, wenn beurteilt werden muss, wie schwer von Lichtpunktefiguren transferierte Gewichte sind. Des Weiteren wurde die Studie durchgeführt, um Hirnstrukturen zu identifizieren, die sich zwischen zwei verschiedenen Bewegungen („manueller Transfer" als Bewegung mit Einbezug des Schulterbereiches und „Rotation des Rumpfes" mit Einbezug des unteren Rückens) mit jeweils zwei unterschiedlich schweren Objekten unterscheiden.

Für die Beantwortung der Frage, welche Gehirnregionen bei der Gewichts-Schätzaufgabe aktiviert sind, wurden die beiden Bedingungen, in denen biologische Bewegung gezeigt wurde, in einem BOLD (Blood Level Oxygen Dependent)-Kontrast mit einer Bedingung verglichen, in der Lichtpunkte ohne den Aspekt biologischer Bewegung dargeboten wurden. Es zeigten

sich Aktivierungen in Regionen, die für die Beurteilung biologischer Bewegung kennzeichnend sind sowie in Regionen, die mit der Verarbeitung von Schmerz in Verbindung gebracht werden. Bei einem Teil dieser Regionen, etwa dem anterioren zingulären Kortex und der Insula, handelt es sich um dieselben Areale. Um die Frage zu beantworten, wie sich die Aktivierungen zwischen den beiden Bewegungen „manueller Transfer“ und „Rotation des Rumpfes“ unterscheiden, wurde ein BOLD-Kontrast zwischen den entsprechenden Bedingungen gerechnet: Bei der Bewegung, die vorrangig den Schulterbereich einbezog, waren Bereiche von S1 aktiviert, die somatotop Hand und Arm repräsentieren. Bei der Bewegung, die vorrangig den unteren Rücken einbezog, war S1 im Bereich der somatotopen Repräsentation des Rückens aktiviert.

Dass bei der Verarbeitung der Gewichts-Schätzaufgabe Hirnregionen aktiviert werden, die auch mit der Verarbeitung von Schmerz in Verbindung gebracht werden, lässt die Hypothese zu, dass auf Ebene dieser Strukturen eine Wechselwirkung zwischen der herabgesetzten Diskriminationsleistung bei chronischen Rücken- bzw. Schulterschmerzpatienten und ihrem chronischen Schmerzleiden stattfindet. Die Ergebnisse zeigen weiterhin, dass verschiedene somatosensorische Netzwerke in Abhängigkeit davon rekrutiert werden, welche Körperregion in die zu beurteilende Bewegung einbezogen ist. Daher gibt es im entsprechenden Bereich von S1 möglicherweise eine Wechselwirkung zwischen Schmerzverarbeitung und der Bearbeitung der Gewichts-Schätzaufgabe. Dies könnte als Erklärung dafür dienen, weshalb in einer vorausgegangenen Studie von de Lussanet et al. (2012) die Diskriminationsleistung von Rückenschmerzpatienten in ihrem betroffenen Areal eingeschränkt war, jedoch keine Einschränkung bestand, wenn die Bewegung Körperregionen involvierte, die nicht von chronischem Schmerz betroffenen waren (de Lussanet et al., 2013).

Manuskript 2: „Human brain stem structures respond differentially to noxious heat”

Die Empfindung von Schmerz wird durch das körpereigene, zentralnervös vermittelte, absteigende Schmerzhemmsystem moduliert. Bei chronischem (Rücken-) Schmerz ist die absteigende Schmerzhemmung wahrscheinlich gestört (Bingel et al., 2007; Staud, 2011). Wesentliche Strukturen der absteigenden Schmerzhemmung wie PAG, NRD und RVM sind, wie bereits im Abschnitt 2.3 beschrieben, im Bereich des Hirnstamms zu finden. FMRT-Untersuchungen des Hirnstamms erwiesen sich bislang als methodisch aufwändig, weil das zu Artefakten führende physiologische Rauschen in diesem Bereich sehr hoch ist (Beissner,

Deichmann, & Baudrexel, 2011; Beissner, Schumann, Brunn, Eisentrager, & Bar, 2014). Daher sollte für dieses Experiment eine spezielle koronare Schichtlegung im fMRT getestet werden, um besonders die Blutfluss-Artefakte in dieser Region zu kontrollieren.

Aus tierexperimentellen Studien ist bekannt, dass Hitzereize mit unterschiedlich schnellem Anstieg der Temperatur zu unterschiedlichen Aktivierungen von PAG (Lumb et al., 2002; Parry, Macmillan, Koutsikou, McMullan, & Lumb, 2008) und NRM (Lu, Sweitzer, Laurito, & Yeomans, 2004) führen. Diese unterschiedlichen Aktivierungen wurden speziell mit der absteigenden Hemmung von Nervenimpulsen aus Aδ- bzw. C-Fasern in Verbindung gebracht (Lu et al., 2004; Lumb, 2002). Studie 2 hatte zum Ziel, ein Paradigma zur Untersuchung des Hirnstamms für die fMRT zu erproben, das zeigen kann, wie mit unterschiedlicher thermischer Stimulation ein differentes Antwortmuster in für die absteigende Schmerzhemmung wesentlichen Arealen erreicht werden kann. Maßgeblich war, das für chronische Schmerzen besonders relevante C-Faser-System präferentiell zu stimulieren und diese Stimulation zu dokumentieren.

Für die Stimulation wurden Bedingungen mit jeweils fünf aufeinanderfolgenden rampenförmigen Hitzereizen mit entweder steilem oder flachem Anstieg der Temperatur eingesetzt. Für jede einzelne Hitzerampe stieg die Temperatur von einer als warm empfundenen baseline-Temperatur bis zu einer individuell als schmerzhaft empfundenen Hitze an und fiel danach wieder auf die baseline-Temperatur ab. Bei den aufeinanderfolgenden Hitzerampen mit steilem Anstieg kommt das „wind up"-Phänomen (Mendell & Wall, 1965) zum Tragen. Dadurch sollte bei den Hitzerampen mit steilem Anstieg eine präferentielle Stimulation von C-Fasern erreicht werden, während die Reizleitung bei den Hitzerampen mit flachem Anstieg überwiegend durch Aδ-Fasern gewährleistet werden sollte. Entsprechend sollten Hitzerampen steilen Anstiegs mit Begriffen des „zweiten Schmerzes", Hitzerampen flachen Anstiegs mit Begriffen des „ersten Schmerzes" beschrieben werden.

Mit der im Magnetresonanztomographen (MRT) verwendeten Methode war es möglich, Aktivierungen in für die Hypothesen relevanten Hirnstammstrukturen sichtbar zu machen, ohne dafür Artefakt-Korrekturen vornehmen zu müssen, die zusätzliche physiologischen Daten einbeziehen. Nach Stimulation mit Hitzerampen steilen Anstiegs resultierte, verglichen mit der Stimulation mit Hitzerampen flachen Anstiegs, eine stärkere Aktivierung im PAG, im NRM und in der RVM. Dass die Hitzerampen steilen Anstiegs vorrangig mit der Reizleitung und -verarbeitung durch das C-Faser-System assoziiert sein könnte, wird durch die Ergebnisse

des Kurzfragebogens von Beissner et al. (2010) nahegelegt, weil die Beschreibung der entsprechenden Schmerzwahrnehmung mit Begriffen des „zweiten Schmerzes“ erfolgte.
Studie 2 zeigt zum ersten Mal beim Menschen, dass eine Hitzestimulation mit unterschiedlich steilem Anstieg der Temperatur zu differentiellen Aktivierungen in Hirnstammstrukturen führt, die bei der absteigenden Schmerzhemmung eine wesentliche Rolle spielen. Daneben konnte mit Studie 2 gezeigt werden, dass sich die in den verschiedenen Bedingungen wahrgenommene Schmerzqualität zwischen „erstem“ und „zweitem Schmerz“ unterscheidet.

Manuskript 3: “Enhanced Brain Responses to Pain-related Words in Chronic Back Pain Patients and its Relation to Current Pain”

Die Verknüpfung der Empfindung von Schmerz, seiner semantischen Verarbeitung und den damit einhergehenden Aktivierungen von Hirnstrukturen sollte bei chronischen Schmerzpatienten aufgrund ihrer häufigen Konfrontation mit Schmerzen besonders stark ausgeprägt sein. Zum Beispiel konnte gezeigt werden, dass chronische Schmerzpatienten eine höhere Erinnerungsleistung für schmerzbezogene Ereignisse aus ihrem Leben zeigen, wenn sie mehrdeutige Schlüsselwörter vorgegeben bekommen (Huse, Knost, & Flor, 1999). Eck et al. konnten bei chronischen Migränepatienten nachweisen, dass diese eine stärkere Aktivierung als gesunde Kontrollprobanden in unter anderem Schmerz verarbeitenden Strukturen aufwiesen, wenn sie schmerzbezogene Wörter gezeigt bekamen, auch wenn diese verbalen Reize nicht im Fokus ihrer Aufmerksamkeit standen (2011). Für Studie 3 leitete sich das Ziel ab, die Unterschiede der kortikalen Verarbeitung von schmerzassoziiertem und nicht-schmerzassoziiertem verbalen Material zwischen chronischen Rückenschmerzpatienten und gesunden Kontrollprobanden zu vergleichen. Darüber hinaus sollte die Abhängigkeit dieser Unterscheide vom aktuellen Ausmaß des Schmerzes, welches während des Experimentes empfunden wurde, untersucht werden.
Während des Experimentes wurden die Versuchspersonen gebeten, im MRT Vorstellungsbilder zu den dort visuell präsentierten positiven, negativen, neutralen und schmerzassoziierten Wörtern zu generieren. Dies sollte eine explitzite Verarbeitung der Wortbedeutung bewirken. Nach dem Experiment gaben die chronischem Rückenschmerzpatienten an, wie hoch das Ausmaß ihres Schmerzes während des Experimentes war.
Insgesamt zeigt sich in diesem Experiment für schmerzassoziierte Wörter eine stärkere Aktivierung bei chronischen Rückenschmerzpatienten in jenen Strukturen, die unter anderem mit

der Verarbeitung von Schmerz in Zusammenhang gebracht wurden (Apkarian et al., 2005). Besonders interessant ist der schmerzspezifische Kontrast zwischen schmerzbezogenen und negativen Wörtern, weil beide Kategorien eine negative Valenz aufweisen und mit hohem Arousal einhergehen. Für diesen Kontrast ergeben sich im Gruppenvergleich zwischen chronischen Rückenschmerzpatienten und gesunden Kontrollprobanden Aktivierungsunterscheide bilateral in der anterioren Insula, im posterioren mittleren zingulären Kortex, sowie im Orbitofrontalkortex. Diese Hirnareale sind bei den chronischen Rückenschmerzpatienten jeweils höher aktiviert. Mit Ausnahme des posterioren mittleren zingulären Kortex sind diese Strukturen auch im Gruppenkontrast beim Vergleich zwischen schmerzbezogenen und den übrigen Wortkategorien bei den chronischen Rückenschmerzpatienten höher aktiviert.
Der Einfluss des aktuellen Ausmaßes des Schmerzes in der Gruppe der chronischen Rückenschmerzpatienten wurde mit der Korrelation zwischen der im MRT angegebenen Schmerzstärke und der BOLD-Antwort in den einzelnen Kontrasten überprüft. Die Schmerzstärke korreliert bspw. im Kontrast schmerzbezogene Wörter zu allen anderen Wortkategorien mit dem subgenualen anterioren zigulären Kortex.

Die höhere Aktivierung der Insula bei den chronischen Rückenschmerzpatienten deutet darauf hin, dass diese eine gesteigerte Bewusstheit für die potentiell schmerzhaften und deshalb bedrohlichen Reize in ihrer Umwelt aufweisen, weil diese Struktur unter anderem die Salienz von Reizen verarbeitet (Legrain et al., 2011; Wiech, Lin, Brodersen, Bingel, Ploner, & Tracey, 2010), an der Überwachung der Unversehrtheit des Körpers Anteil hat (Craig, 2009; Weiss et al., 2008) und an der Ausrichtung des Aufmerksamkeitsfokus beteiligt ist (Iannetti et al., 2008). Die gleichzeitige Aktivierung des posterioren mittleren zigulären Kortex könnte ein weiterer Hinweis darauf sein, dass die schmerzbezogenen Wörter für Rückenschmerzpatienten eine höhere Salienz aufweisen (Wiech et al., 2010). Die Rolle des Orbitofrontalkortex wird unter anderem darin gesehen, den Verstärkerwert von Reizen zu verarbeiten und daraus die Richtung des Handelns abzuleiten (Kringelbach & Rolls, 2004; Kulkarni, Bentley, Elliott, Youell, Watson, Derbyshire, Frackowiak, Friston, & Jones, 2005; Lorenz, Cross, Minoshima, Morrow, Paulson, & Casey, 2002; Wiech, Seymour, Kalisch, Stephan, Koltzenburg, Driver, & Dolan, 2005). Negative (visuelle) Reize führten zu höheren Aktivierungen dieser Struktur als positive (Roy, Piche, Chen, Peretz, & Rainville, 2009). Die höhere Aktivierung des Orbitofrontalkortex bei den chronischen Rückenschmerzpatienten könnte sich daraus erklären, dass schmerzbezogene Wörter bei dieser Gruppe häufiger mit einem aktuellen Auftreten chronischen Schmerzes assoziiert wurden, der Verstärkerwert dieser ohnehin negativ konnotierten

Wörter dadurch weiter stieg, d.h. noch negativer wurde, und folglich die affektive Auseinandersetzung mit diesen Stimuli gesteigert wurde.

Die Schmerzstärke korreliert im Kontrast schmerzbezogene Wörter zu allen anderen Wortkategorien mit dem subgenualen anterioren zigulären Kortex. Diese Struktur spielt eine wichtige Rolle bei der emotionalen Verarbeitung von Reizen und könnte in diesem Zusammenhang den Fokus der Aufmerksamkeit umso mehr zu den bedrohlichen und salienten schmerzassoziierten Wörtern lenken (Richter et al., 2010), je stärker die aktuellen Schmerzen während der Präsentation der Reize waren.

Insgesamt können die Ergebnisse von Studie 3 als ein Beleg für die neuronale Netzwerktheorie im Sinne der im Abschnitt 2.1 beschriebenen Hebb‘schen Zellbverbände gelten. Sie zeigen den besonderen Einfluss schmerzassoziierter Umweltreize auf die Schmerzverarbeitung bei chronischen Rückenschmerzpatienten.

Diese Ergebnisse von Studie 3 ordnen sich in die bisherige Literatur ein (Eck et al., 2011; Richter et al., 2010); sie zeigen einen klaren Einfluss chronischen unspezifischen Rückenschmerzes auf die Verarbeitung schmerzbezogener, aber nicht-noxischer Reize. Studie 3 erweitert die bisherige Fachliteratur um die Erkenntnis, dass ein höheres Ausmaß aktuellen Schmerzes Aktivierungen durch schmerzbezogene verbale Reize in einigen schmerzverarbeitungsrelevanten Hirnstrukturen noch steigert.

4 Diskussion, Limitationen und Ausblick

Wie bereits aus der Einleitung hervorgeht, sind chronische Rückenschmerzen mit kognitiven Mechanismen assoziiert, die ihr Auftreten beeinflussen oder durch ihr Auftreten verändert werden. Für die weitere Erforschung und für die Ableitung eines umfassenden Modells dieser Erkrankung ist eine Offenlegung dieser Bezüge notwendig. Nach einer Zusammenführung der Ergebnisse nach Maßgabe der Zielstellung dieser Arbeit und einem Ausblick auf weitere Anwendungsmöglichkeiten der verwendeten Methoden sowie auf zukünftige Forschung zu diesem Gegenstand sollen mögliche Einschränkungen aufgezeigt werden, die durch die angewendeten Methoden begründet sind.

Die drei in dieser Arbeit zusammengefassten Studien zeigen Möglichkeiten auf, wie mithilfe der fMRT in Erfahrung gebracht werden kann, welche spezifischen Wechselwirkungen es unter anderem zwischen chronischem Rückenschmerz und einer kognitiven Reizverarbeitung geben kann. Sowohl bei gesunden Kontrollpersonen als auch bei chronischen Rückenschmerzpatienten wird die Möglichkeit einer Beeinflussung des Schmerzgeschehens durch Verarbeitungsprozesse im ZNS und vice versa durch die Ergebnisse der hier aufgeführten Studien gestützt. Studie 1 und Studie 2 wurden durchgeführt, um die Tauglichkeit des experimentellen Vorgehens für nachfolgende Untersuchungen an Rückenschmerzpatienten zu testen und um Aufschluss darüber zu erhalten, wie gesunde Kontrollpersonen die angewendeten schmerzbezogenen und schmerzhaften Reize neuronal verarbeiten. In Studie 3 wurden im Unterschied dazu chronische Rückenschmerzpatienten mit einer entsprechend angepassten Kontrollgruppe verglichen.

Studie 1 konnte zeigen, dass verschiedene somatosensorische Netzwerke zur Beurteilung von Aspekten der Bewegung rekrutiert werden. Bewegungen unter Einbeziehung des Rückens bzw. unter Einbeziehung des Schulterbereiches aktivieren jeweils die korrespondierenden somatotopen Bereiche in S1. Dieser Befund stellt wichtige Informationen für das Verständnis der Gewichts-Schätzaufgabe bereit. Wenn der gesamte Körper in die zu beurteilende Bewegung einbezogen ist, werden jeweils nur die Regionen in S1 aktiviert, die für die zu beurteilende Bewegung wesentlich sind. Daneben geben die Ergebnisse von Studie 1 wichtige Anhaltspunkte, weshalb die Diskriminationsleistung von Patienten mit chronischem Rückenschmerz bei der Beurteilung des durch eine Rumpfbewegung gehobenen Gewichtes vermindert (de Lussanet et al., 2013) sein könnte. Wenn die Aufgabe, das gehobene Gewicht bei einer

Bewegung mit Einbeziehung des Rückens zu schätzen, bei den Probanden jene Teile von S1 aktiviert, die den Rücken repräsentieren, so ist es denkbar, dass diese kortikale Repräsentation des Rückens in S1 bei Patienten mit Schmerzen in dieser Körperregion verändert ist. Diese Hypothese wäre auch begründbar, weil in S1 neben der somatosensorischen Information auch Aspekte des Schmerzes, wie etwa die Lokalisierung der Noxe und die Diskriminierung der Schmerzintensität verarbeitet werden (Bushnell, Duncan, Hofbauer, Ha, Chen, & Carrier, 1999; Timmermann, Ploner, Haucke, Schmitz, Baltissen, & Schnitzler, 2001; Worthen, Hobson, Hall, Aziz, & Furlong, 2011).

Weiterhin sind bei der Beurteilung der transferierten Gewichte aus der Bewegung der Lichtpunktefiguren Strukturen wie der anteriore zinguläre Kortex, die Insula und S2 sowie Teile des Kleinhirns aktiviert, die auch mit Schmerzverarbeitung in Verbindung gebracht werden (Apkarian et al., 2005; Peyron, Laurent, & Garcia-Larrea, 2000; Weiss, Straube, Boettcher, Hecht, Spohn, & Miltner, 2008). Daher scheint es möglich, dass die schlechtere Diskrimination der Gewichte bei chronischen Rückenschmerzpatienten in der Studie von de Lussanet et al. (2013) Folge einer Wechselwirkung zwischen der Beurteilung der Gewichte und einer durch chronischen Rückenschmerz veränderten Schmerzverarbeitung in einer oder mehrerer dieser Regionen ist. Weil die schlechtere Diskriminationsleistung bei chronischen Rückenschmerzpatienten nur für die Rumpfbewegung und bei chronischen Schulterschmerzpatienten nur für eine Bewegung mit Einbezug des Schulterbereiches gefunden wurde (de Lussanet et al., 2012), ist jedoch wahrscheinlich davon auszugehen, dass die gegenseitige Beeinflussung auf Ebene von S1 und S2 geschieht, weil diese Strukturen jeweils als Homunkulus organisiert sind. So wird innerhalb dieser Strukturen die eingehende Information aus verschiedenen Körperteilen entsprechend an verschiedenen Orten unabhängig voneinander verarbeitet, was der fokal herabgesetzten Diskriminationsleistung bei Schulter- und Rückenschmerzpatienten entsprechen würde. Für eine Modulation auf Ebene von S1 spräche des Weiteren, dass bei chronischen Rückenschmerzpatienten für diese Struktur eine größere kortikale Dicke (Kong et al., 2013) und eine geringere funktionelle Konnektivität (Friston, 2011) als bei gesunden Kontrollprobanden gefunden wurde (Kong et al., 2013).

Überraschenderweise konnten die gesunden Probanden in Studie 1 die Gewichtsunterschiede nicht richtig einschätzen, weshalb sich auch keine Unterschiede in der BOLD-Antwort im Kontrast der beiden gehobenen Gewichte finden ließen. Dies steht im Widerspruch zu ähnlichen Studien, in denen die Probanden die gehobenen Gewichte gut diskriminieren konnten (de Lussanet et al., 2013; de Lussanet et al., 2012; Runeson & Frykholm, 1981). Auch in einer

Vorstudie zu Studie 1 außerhalb des MRT konnten die Probanden die Gewichte diskriminieren. In einem nachfolgenden Kontrollexperiment außerhalb des MRT konnten die Versuchspersonen die Gewichte auch dann diskriminieren, wenn sie sich in einer liegenden Position befanden sowie wenn sie gebeten wurden, sich nicht zu bewegen, um Aspekte der Situation im MRT nachzustellen. Möglicherweise haben das im MRT allgemein erhöhte Arousal und die Geräuschkulisse dazu beigetragen, dass die Probanden die Aufgabe nicht richtig erfüllen konnten. Für die Einordnung der Ergebnisse ist daher zu bedenken, dass die gefundenen fMRT-Aktivierungen für die Durchführung der Gewichts-Schätzaufgaben notwendig, für ihre korrekte Bearbeitung jedoch nicht hinreichend sind.
Das genutzte experimentelle Vorgehen ist möglicher Anknüpfungspunkt für eine nachfolgende Studie, in der chronische Rückenschmerzpatienten mit gesunden Kontrollpersonen verglichen werden können.

Studie 2 hatte ergeben, dass mit rampenförmigen Hitzereizen unterschiedlicher Anstiegssteilheit, die wiederholt direkt hintereinander präsentiert werden, verschiedene Wahrnehmungsqualitäten des Schmerzes resultieren. Bei den Hitzereizen mit schnellem Anstieg der Temperatur wurde die Wahrnehmung mit Begriffen des zweiten Schmerzes beschrieben, bei Hitzereizen mit langsamen Anstieg mit Begriffen des ersten Schmerzes. Im Vergleich zu der Stimulation mit Hitzereizen mit flachem Anstieg der Temperatur zeigten sich für die Hitzereize mit steilem Anstieg der Temperatur höhere Aktivierungen im PAG, im NRD und in der RVM. Mit Studie 2 ist zum ersten Mal eine spezielle koronare Schichtlegung zur Untersuchung des Hirnstamms zur Anwendung gekommen. Es ist mit dieser Methode möglich gewesen, die für die Hypothesen relevanten Aktivierungen in diesem Bereich des ZNS zu untersuchen, ohne weitere Korrektur-Algorithmen zur Verringerung der Artefakte einzusetzen, die aus der Bewegung der Blutgefäße, der Zerebrospinalflüssigkeit und der Atmung resultieren.
Die Ergebnisse von Studie 2 sprechen für eine mögliche präferentielle Stimulation der beiden schmerzleitenden Fasersysteme durch Hitzestimulation mit unterschiedlicher Anstiegs-Steilheit der Temperatur sowie für eine differentielle Stimulation in wichtigen Teilen des absteigenden Schmerzhemmsystems. Studie 2 schafft methodischen Grundlagen, zukünftig bei chronischen Rückenschmerzpatienten speziell nach Auffälligkeiten in einem wesentlichen Teil des absteigenden Schmerzhemmsystems zu suchen. Außerdem ist mit dem beschriebenen experimentellen Vorgehen gewährleistet, die besondere Rolle der Aufrechterhaltung des „zweiten“, für chronische Schmerzen bedeutsamen Schmerzes zu erforschen.

Die in Studie 3 untersuchten Patienten mit chronischem unspezifischen Rückenschmerz zeigten ein stärkeres neuronales Antwortverhalten als gesunde Kontrollprobanden in schmerzverarbeitungsrelevanten Hirnstrukturen beim Lesen schmerzassoziierter Wörter, wenn diese mit Valenz- und Arousal-angepassten negativen Wörtern verglichen wurden. Es war bereits bekannt, dass die anhaltende Empfindung von Schmerz eine erhöhte Empfänglichkeit für schmerzassoziierte Informationen (Flor, Braun, et al., 1997; Flor, Knost, & Birbaumer, 2002), z. B. für verbale Reize (Flor, Knost, & Birbaumer, 1997), mit sich bringt. Studie 3 zeigt auf, dass diese Sensitivierung bei Patienten mit chronischem unspezifischem Rückenschmerz ebenfalls vorhanden ist. Darüber hinaus wird gezeigt, welches neuronale Substrat bei dieser Patientengruppe der Verarbeitung der schmerzbezogenen verbalen Stimuli zugrunde liegt. Höhere Aktivierungen fanden sich in Übereinstimmung mit relevanten Vorarbeiten (Eck et al., 2011; Richter et al., 2010) bspw. beim Gruppenvergleich zwischen Patienten und Kontrollen für den Kontrast zwischen schmerzbezogenen und negativen Wörtern in der Insula und in Teilen des zingulären Kortex. Diese Aktivierungen deuten darauf hin, dass chronische Rückenschmerzpatienten eine stärkere attentionale Fokussierung und eine emotionalere Verarbeitung der schmerzbezogenen Wörter aufweisen könnten.
Es konnte erstmalig gezeigt werden, dass die während des Experimentes aufgetretenen Schmerzen in einem linearen Zusammenhang mit einigen der gefundenen Aktivierungen stehen. Der aktuell empfundene Schmerz könnte demnach eine Auswirkung auf die zeitgleiche Verarbeitung schmerzbezogener Wörter haben. Es wäre wünschenswert, das experimentelle Vorgehen dieser Studie noch bei Patientengruppen mit anderen chronischen Schmerzzuständen oder akutem Schmerz anzuwenden, um herauszufinden, ob sich die Ergebnisse und ihre Deutung generalisieren lassen. Daneben wäre eine Untersuchung denkbar, bei der die schmerzassoziierten verbalen Reize nicht im Fokus der Aufmerksamkeit stehen, um die Abhängigkeit der gezeigten Ergebnisse von der Aufmerksamkeitszuwendung zu erforschen.

Limitationen

An Studie 1 und 2 ist zu kritisieren, dass an diesen Untersuchungen ausschließlich Studenten teilgenommen haben und sich somit die Möglichkeit einer Generalisierung der Ergebnisse auf die Gesamtbevölkerung in nachfolgenden Arbeiten mit entsprechenden Patienten- und Kontrollgruppen erst herausstellen muss. Insbesondere chronische Schmerzpatienten

weisen in der Regel ein deutlich höheres Durchschnittsalter sowie eine andere Schmerzwahrnehmung und -bewertung auf (Hauser et al., 2013; Staud et al., 2007). Auch für Studie 3 muss man einschränken, dass die Stichprobengröße gering ist.

Für die fMRT Aufnahme wäre es in allen Studien wünschenswert, die räumliche Auflösung weiter zu erhöhen. Eine weitere Differenzierung besonders der in Studie 2 untersuchten kleinen Strukturen im Hirnstamm, die bei der aktuellen Auflösung von 2x2x2 mm nicht eindeutig vorgenommen werden kann, wäre für die Interpretation der Ergebnisse wichtig. Für eine noch genauere Charakterisierung der in Studie 1 gefundenen Somatotopie in S1 sowie für die möglicherweise ebenfalls eine Somatotopie abbildende Aktivierung in S2 (Eickhoff, Grefkes, Zilles, & Fink, 2007) gilt das in gleicher Weise. Dies sollte mit den in den letzten Jahren rasant weiterentwickelten „high resolution"-fMRT-Sequenzen (Goense, Merkle, & Logothetis, 2012; Johnson, Suzuki, & Rugg, 2013; Koopmans, Boyacioglu, Barth, & Norris, 2012; Sun, Gardner, Costagli, Ueno, Waggoner, Tanaka, & Cheng, 2013) jedoch ohne weiteres möglich sein.

Daneben ist eine Erhöhung der zeitlichen Auflösung der funktionellen Sequenzen wünschenswert, da entsprechende Techniken mittlerweile zu Verfügung stehen (Feinberg & Yacoub, 2012; Gibson, Peters, & Bowtell, 2006). Hieraus ergäbe sich besonders gut die Möglichkeit einer Analyse der funktionellen und effektiven Konnektivität (Friston, 2011; Stephan & Friston, 2010), die möglicherweise zwischen den gefundenen Strukturen in allen drei Studien besteht. Anhand der funktionellen Konnektivität könnte die Interpretationen der Ergebnisse spezifischer gestaltet werden, welche sonst vorrangig durch zirkuläre Bezugnahmen zu anderen Studien in diesem Feld vorgenommen wird.

Weil es chronischen Rückenschmerzpatienten schwer fällt, längere Zeit mit der Aufforderung, sich nicht zu bewegen, ruhig im MRT zu liegen, wäre es für Studie 2 möglich, das Paradigma von derzeit knapp zwanzig Minuten Dauer auf etwa die Hälfte der Zeit zu reduzieren, indem man die Bedingung mit der nicht schmerzhaften Stimulation entfallen ließe. Dies hätte für die Auswertung und Interpretation der Ergebnisse vernachlässigbare Folgen. Für die beiden anderen Studien gibt es diese Möglichkeit nicht; hier sollte besonders darauf geachtet werden, dass der Kopf der Patienten im MRT gut fixiert ist, da Bewegungen bei einem schmerzenden Rücken kaum ausbleiben können.

Weil sich in Studie 3 bereits eine Abhängigkeit der neuronalen Aktivierungen vom aktuellen Schmerz zeigte, wäre es wichtig, ein solches Maß auch in die Paradigmen von Studie

1 und 2 einzubringen, wenn mit diesen chronische Rückenschmerzpatienten mit aktuell vorhandenem Schmerz untersucht werden. In Studie 3 ist der aktuelle Schmerz retrospektiv, d. h. im direkten Anschluss an das Experiment erfragt worden. Hier wäre eine Verbesserung insofern denkbar, als dass man den Patienten bereits im MRT die Möglichkeit gibt, in kurzen zeitlichen Abständen ihren aktuellen Schmerz anzugeben. Mit diesen Daten könnte man den Einfluss des aktuellen Schmerzes und die damit einhergehenden Aktivierungsunterscheide besser charakterisieren.

Studie 3 und 1 gingen explorativ vor; Studie 2 wendete ein konfirmatorisches Vorgehen an, berichtet jedoch auch über Ergebnisse, die aus einer Exploration der Daten hervorgegangen sind. Die gefundenen Ergebnisse bedürfen also noch einer Replikation. Bei Studie 3 ist darüber hinaus kritisch zu beurteilen, dass die Hypothesen vorrangig unter Gesichtspunkten des vormals aktuellen Erkenntnisstandes aufgestellt wurden und nicht sparsam genug gefasst waren. Die Hypothese, dass durch die schmerzassoziierten Wörter Teile der Neuromatrix des Schmerzes aktiviert werden können, ist schwer falsifizierbar, da dieses Netzwerk auch bei der Verarbeitung nicht-schmerzassoziierter Information und Reizmerkmalen wie Salienz aktiviert ist (Iannetti & Mouraux, 2010).

In Studie 3 ist weiterhin nicht klar, ob die bei chronischem Rückenschmerz veränderten Aktivierungen Folge oder Voraussetzung der Schmerzerkrankung sind und womit die intraindividuelle zeitliche Veränderung der Schmerzwahrnehmung assoziiert ist. Darüber kann nur eine Längsschnittuntersuchung, beispielsweise an besonders gefährdeten Berufsgruppen wie etwa Kranken- und Altenpflegern, Erkenntnisse vermitteln.

Es wäre weiterhin zu bedenken, sowohl in Studie 3 als auch in nachfolgenden Arbeiten auf Grundlage von Studie 1 und 2, die Varianz der Depression, die in der Gruppe der chronischen Rückenschmerzpatienten signifikant höher ausfällt als bei gesunden Kontrollprobanden, aus dem der fMRT-Analyse zugrundeliegenden General Linear Model (GLM) herauszupartialisieren. Es ist jedoch darauf hinzuweisen, dass Depression der stärkste Prädiktor für chronischen Schmerz ist (Apkarian, Baliki, & Geha, 2009) und die Korrelation der beiden Konstrukte mit r=0.4 entsprechend hoch ausfällt (Meyer, Cooper, & Raspe, 2007). Wenn demnach die Varianz der Depression aus den Daten entfernt wird, ist es nicht auszuschließen, dass im selben Zuge auch die interessierende Varianz des Konstrukts „chronischer Schmerz“ vermindert wird und die so bereinigten Daten keinen Erkenntnisgewinn mehr über die damit einhergehenden Phänomene zulassen.

Zusätzliche Einschränkungen müssen für Studie 2 hinsichtlich der unterschiedlichen Länge der Stimulationsblöcke sowie bezüglich des unterschiedlichen Betrags der über die Thermode auf die Haut übertragenen Energie in den beiden Bedingungen gemacht werden. Die Länge der Stimulationsblöcke hängt direkt mit den für das Paradigma notwendigen Frequenzen der Hitze-Stimulationen zusammen. So war die Gesamtlänge eines Stimulationsblocks in der Bedingung mit dem flachen Anstieg der Temperatur größer als in der Bedingung mit dem steilen Anstieg der Temperatur.

Eine mögliche Alternative, die Gesamtlänge der Hitze-Stimulation bei steilem Temperaturanstieg an die Bedingung des flachen Temperaturanstiegs anzupassen, wäre das Einbauen weiterer Hitzerampen in die Blöcke mit steilem Temperaturanstieg. Allerdings hätte die Verwendung zusätzlicher schmerzhafter Hitzerampen den Nachteil einer verringerten Vergleichbarkeit der beiden Bedingungen, da eine Erhöhung der Anzahl schmerzhafter Stimuli eventuell auch mit einem veränderten Ausmaß des Schmerzes einhergeht.

In der Bedingung mit dem flachen Anstieg wird insgesamt mehr Energie auf die Haut übertragen als in der Bedingung mit dem steilen Anstieg. Diesen Effekt könnte man z.B. verhindern, indem man den Temperaturanstieg in der Bedingung mit der niedrigeren Hitze-Stimulationsfrequenz ebenfalls steil wählt. Um die niedrigere Frequenz beizubehalten, müsste die Temperatur zwischen den Hitzerampen länger auf dem Grundniveau bleiben. Allerdings würde bei dieser Variante die Habituation der Wärmerezeptoren im Vergleich zu der im Experiment verwendeten Bedingung mit dem steilen Temperaturanstieg niedriger ausfallen. Hierbei ist nochmals hervorzuheben, dass die nozizeptiven Rezeptoren erst ab einer Temperatur von 43 °C feuern (Julius & Basbaum, 2001) und somit auch die Hitzereize erst ab der Überschreitung dieser Temperaturschwelle für die Schmerzwahrnehmung bedeutsam sind. Der Unterschied in der Energieübertragung oberhalb der Schwelle von 43 °C ist im Vergleich der beiden Bedingungen deutlich geringer als wenn das Integral unter der gesamten Hitzerampe in Betracht gezogen wird. Deshalb gehen wir davon aus, dass diese Unterschiede nicht von entscheidender Bedeutung für die Ergebnisse von Studie 2 waren.

Weiterhin tritt bei der Hitzestimulation mit unterschiedlicher Anstiegs-Steilheit eine teilweise Koaktivierung der an der Nozizeption beteiligten Fasertypen auf. Dies kann als Nachteil gesehen werden, wenn man ausschließlich an der Funktion der C-Fasern interessiert ist. Andererseits entspricht eine präferentielle Stimulation der Fasersysteme stärker einer natürlichen Schmerzerfahrung, die ebenfalls Folge einer Aktivierung mehrerer verschiedener Nozizeptoren ist.

Fazit

Studie 1 und 2 liefern methodische Grundlagen für die Testung spezifischer Hypothesen bzgl. einer Einflussnahme zentralnervöser Verarbeitungsprozesse auf die Wahrnehmung und Aufrechterhaltung chronischer Rückenschmerzen. Studie 1 hält wichtige Informationen zum Verständnis der Gewichts-Schätzaufgabe bereit und zeigt wahrscheinlich, weshalb diese Aufgabe von chronischen Rückenschmerzpatienten schlechter erfüllt werden kann als von gesunden Kontrollpersonen. Mit dem in Studie 2 gezeigten Paradigma gelingt es, entscheidende Strukturen im Hirnstamm differentiell zu aktivieren, die bei der Modulation von (chronischen) Schmerzen beteiligt sind. Studie 3 zeigt, dass chronischer Rückenschmerz Einfluss auf die kognitive Verarbeitung von schmerzassoziierten Reizen haben kann. Hier sind schmerzverarbeitungsrelevante Hirnstrukturen bei chronischem Rückenschmerz in der Tendenz höher aktiviert oder zeigen eine veränderte Funktionalität. Die Ergebnisse verweisen auf eine Anpassung neuronaler Prozesse im ZNS an den chronischen Rückenschmerz.

Für alle Studien erwies sich die fMRT als geeignete Methode, entsprechende Prozesse im ZNS abzubilden.

5 Übersicht zu den Manuskripten

Manuskript I:

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Brain activity for visual judgment of lifted weight

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ABSTRACT

It is well established that humans can recognize high-level aspects from point-light biological motion, such as gender and mood. If the task is to judge the manipulated weight we expected that sensorimotor regions should be recruited in the brain. Moreover, we have recently shown that chronic pain in a limb that is involved in the presented movement disturbs the weight judgment. We therefore hypothesized that some cortical regions usually activated during the processing of pain will also be activated while viewing point-light biological motion with the instruction to judge the manipulated weights. We investigated point-light biological motion of two types of movements performed with different weights in a blocked fMRI experiment in healthy subjects. In line with our a priori hypothesis, we found strong activity in the regions known as the neuromatrix of pain, such as the anterior cingulate (ACC), insula, as well as primary and secondary somatosensory regions. We also found activation in the occipital and temporal regions that are typical for biological motion, as well as regions in the cerebellum and prefrontal cortex. The activation of the somatosensory regions probably serves the judgment of the biological motion stimuli. Activation of the anterior cingulate and the insula might be explained by their role in the integration of behaviorally relevant information. Alternatively, these structures are known to be involved in the processing of nociceptive information and pain. So it seems possible that the interference between judgment of weights and perception of pain in chronic pain patients occurs in the somatosensory areas, anterior cingulate and/or insula. This finding provides important information as to the underlying mechanisms used for the weight judgment task, but also why chronic pain interferes with this task.

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1. Introduction

Point-light biological motion is a highly impoverished visual display of human movements (Johansson, 1973). Interestingly, this kind of stimuli are easily recognized in such detail that naive observers spontaneously report how many people are displayed and what each of them does. In an experimental setup subjects can judge the weight of an object that is manipulated by the actor in the point-light display (Runeson & Frykholm, 1981). Since this early study the weight-judging task has been used frequently, especially because it provides an interesting link between the visual and the sensorimotor systems (Alaerts, Swinnen, & Wenderoth, 2010; Auvray, Hoellinger, Hanneton, & Roby-Brami, 2011; Bingham, 1987; Bosbach, Cole, Prinz, & Knoblich, 2005; de Lussanet et al., 2012; Hamilton, Wolpert, & Frith, 2004; Marquez, Ceux, & Wenderoth, 2011; Poliakoff, Galpin, Dick, & Tipper, 2010; Shim, Carlton, & Kim, 2004). However, although a number of these studies applied transcranial magnetic stimulation (TMS) (Alaerts et al., 2010; Marquez et al., 2011; Senot et al., 2011), no study has yet addressed the brain activity that is evoked by the task of judging weight from visually perceived stimuli. The visual observation of actions activates regions in the premotor and inferior parietal cortex (Rizzolatti & Craighero, 2004). The measurement of brain activity from imaging studies to biological motion is well established in a large number of studies, which have typically found blood oxygen level dependent (BOLD) activity in occipital, temporal, and intraparietal regions (Grossman et al., 2000). BOLD activity in premotor and somatosensory regions has been found as well for point-light biological motion stimuli (Saygin, Wilson, Hagler, Bates, & Sereno, 2004).

Motion and its perception are strongly affected in individuals suffering from chronic pain (de Lussanet et al., 2012, 2013). Chronic pain patients strongly change the way they move and coordinate (Hodges & Tucker, 2011). Also, patients with chronic pain often suffer from kinesiophobia and depression (Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995). Despite these changes in chronic pain patients, it is known that changes in the brain are detectable. Structures typically involved are the anterior cingulate cortex (ACC), the insula, somatosensory regions (primary and secondary somatosensory cortex SI and SII), and the cerebellum (Apkarian, Bushnell, Treede, & Zubieta, 2005; Price, 2000). Thus, chronic pain is associated with problems of the sensorimotor system as well as with altered processes and structures in the brain.

It is well accepted that chronic pain may interfere with high-level cognitive processes (Kunz, Prkachin, & Lautenbacher, 2009; Rainville et al., 2011; Seminowicz & Davis, 2007). For example, pain-related words are processed differently in different populations of chronic pain patients (Eck, Richter, Straube, Miltner, & Weiss, 2011; Weiss, Miltner, & Dillmann, 2003). Also, patients with chronic back pain are specifically impaired when judging the manipulated weight from visually presented actions (de Lussanet et al., 2013). Due to this impairment chronic pain patients cannot judge the differences in the manipulated weight if the movement involves the body part that is affected in the patient (de Lussanet et al., 2012, 2013). In the latter study, two kinds of movements were presented with a range of different weights: manual transfer where a weight was transferred from the right to the left side using the upper extremities (Fig. 1B) and a trunk rotation where a weight is lifted and transferred from the right to the left side using the whole body (Fig. 1A). Subjects with shoulder pain were specifically impaired in weight assessment for manual transfer while subjects with low back pain were specifically impaired in weight assessment for trunk rotation.

How can this result be explained? We hypothesized that chronic pain interferes with the cortical regions that are usually recruited when viewing point-light biological motion with the instruction to judge the manipulated weights. We expected that the weight judgment task in healthy subjects should recruit the brain regions that are known to be affected in chronic pain patients. Thus, the goal of the present study was to measure the BOLD activity of healthy subjects in a functional MRI (fMRI) experiment during the presentation of point-light biological motion where different weights were lifted with the task to rate these weights.

We aimed to characterize the structures that are activated during the weight lifting tasks. We were also interested in the difference of activation between the two different kinds of movement, i.e., manual transfer versus trunk rotation. Finally, we wanted to compare those structures activated during the

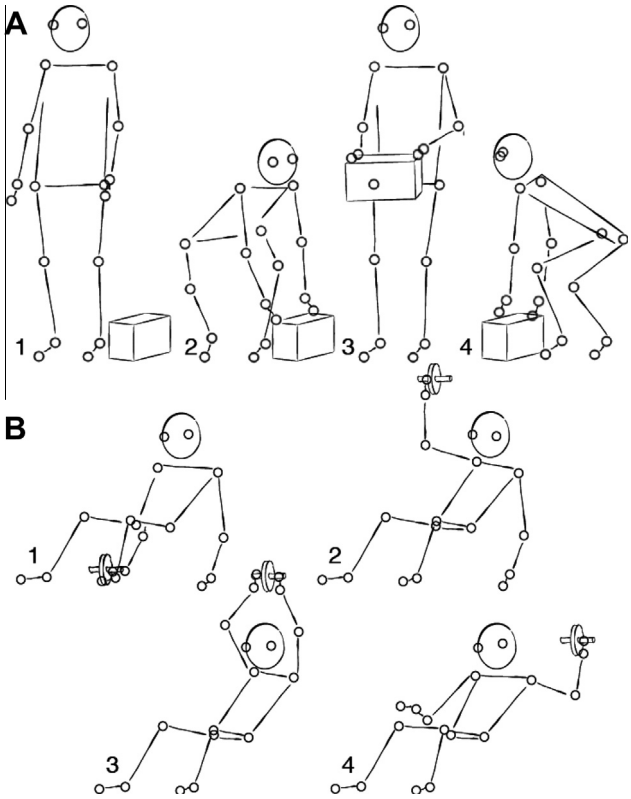

Fig. 1. Static representations of two of the point-light stimuli. (A) Trunk rotation. (B) Manual transfer. In the experiments only the points were visible; the connecting lines are for illustrative purpose only.

assessment of lifted weights with structures belonging to the neuromatrix of pain (Apkarian et al., 2005).

2. Methods

2.1. Subjects

Fifteen healthy, right-handed (Oldfield, 1971) subjects (2 male, 13 female, 19–31 years) volunteered in the fMRI experiment. Subjects were informed about the procedure of the experiment and provided written informed consent. The experiment used movies with either a trunk rotation or a manual transfer movement of weights in two classes to investigate the activation of the brain by means of fMRI. No subject had a history of neurological, psychiatric or pain disorder. Subjects were paid €6 for participating in the experiment. They were free to withdraw from the experiment at any time. The procedure was approved by the local ethics committee of the Friedrich Schiller University.

2.2. Visual stimuli

Computer-animated point-light stimuli (Fig. 1) were computed from recorded kinematic data from two healthy actors (one male and one female; Qualisys Motion Capture Systems) and depicted trunk rotation and manual transfer movements, displayed as white dots moving against a dark background

(Fig. 1). On the day before the recordings each actor practiced the timing of the movement sequences without load, against a metronome. For the recordings, the same movement was performed several times, each time with a different weight, again against the metronome. The actors never knew which weight they were to move. Thus it was secured that the movements of different weights followed exactly the same sequence and had the same timing (de Lussanet et al., 2012). A scrambled version of each scene presented the same dots each with a random offset such that the bounding box of the scene was conserved. The figures depicted in the movies carried different weights determining the four conditions of this experiment: manual transfer movements were presented with 3.5 and 7.5 kg, and trunk rotation movements were presented with 7.5 and 15 kg. The loads in the trunk rotation movements were twice as high as those of the manual transfer movements, so that the load on each hand was the same in each of the movement kinds. The low weights were perceived as "easy" and the heavy ones as "quite difficult" to manipulate by the actor.

2.3. Experimental procedure

The stimuli were projected (Presentation 16.3) via a video beamer onto a screen mounted to the head coil of the scanner. To familiarize the participants with the experimental hardware, each subject received a brief demonstration of the adjusting wheel for the weight rating prior to the experiment. Participants were naive about the purpose of the experiment. The subjects were instructed to focus on the movement of the figures displayed and to estimate the weight of the item moved using the adjusting wheel. The adjusting wheel moved a pointer underneath a scale ranging from 0 to 25 kg in steps of 1 kg. One example of a movie and a subsequent weight rating were presented in order to familiarize the participants with the experimental procedure. Each participant completed one experimental run of 14 minutes duration. The experimental design is displayed in Fig. 2. Each condition, followed by the weight rating, was presented 5 times throughout the experiment. On each trial, the movie sequence was shown twice. The order of the 20 trials (4 different conditions) was pseudo-randomized with the restriction that the same condition was not presented twice in succession. On each trial, the experimental condition was preceded by one movie with scrambled point-light stimuli followed by a 1-s fixation cross.

2.4. Image acquisition

Scanning was performed with a 3T magnetic resonance scanner (Tim Trio, Siemens Medical Systems, Erlangen, Germany). The experiment started with a high-resolution T1-weighted scan of the brain (192 slices, TE = 5 ms, FOV: 256 × 256 mm, resolution: 1 × 1 × 1 mm) for anatomical referencing and visualization. A shimming procedure preceded the succeeding functional MR scanning. The first two volumes were discarded in order to improve field homogeneity. In the experimental fMRI run, 250 volumes were acquired using a T2∗ weighted echo-planar sequence (TE = 61 ms, TR = 3.7 s; FOV = 192 ∗ 192 mm). Each volume comprised 60 slices (2 mm thickness and 2 × 2 mm in-plane resolution) which were prescribed parallel to the AC–PC plane).

2.5. Analysis of behavioral data

Performance data were analyzed with SPSS 13.0 (SPSS Inc., Chicago, IL). The average weight rating scores of each subject for each movement condition were submitted as dependent variable to an

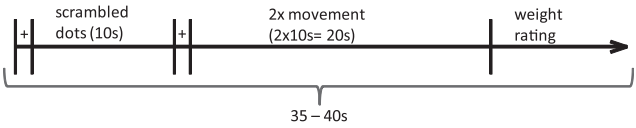

Fig. 2. Time course of one trial of the fMRI paradigm. The fixation cross (+) was presented for 0.6 s. The fixation crosses and the rating mask were preceded by a blank screen of 1.5 s, 0.5 s and 2.0 s respectively.

analysis of variance (ANOVA) with repeated measures on WEIGHT (high versus low) and MOVEMENT (trunk rotation versus manual transfer) as within-subject factors to detect differences regarding the subjective weight estimations between the particular conditions.

2.6. fMRI Preprocessing

Preprocessing and analysis of fMRI data was performed using BrainVoyagerQX 2.1 (Brain Innovation, Maastricht, The Netherlands). Primarily, all volumes were realigned to the first volume in order to minimize effects of head movements on data analysis. Further data preprocessing comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) and temporal smoothing (high pass filter: 4 cycles per run; low pass filter: 2.8 s; linear trend removal) (Richter, Eck, Straube, Miltner, & Weiss, 2010; Straube, Schmidt, Weiss, Mentzel, & Miltner, 2009; Weiss et al., 2008). The anatomical and functional images were co-registered and normalized to the Talairach space (Talairach, 1988).

2.7. fMRI Statistical Analysis

Statistical analyses were performed by multiple linear regression of the signal time course at each voxel. The expected BOLD signal change for each condition (predictor) was modeled by a canonical hemodynamic response function. A random-effects General Linear Model was used to identify associated brain activity in all acquired slices. To minimize false-positive results, we tested whether the detected clusters survived a correction for multiple comparisons (Goebel, Esposito, & Formisano, 2006). Similarly to previous experiments (Richter et al., 2010; Straube et al., 2009; Weiss et al., 2008), we used the approach as implemented in BrainVoyagerQX2.4, which is based on a 3D extension of the randomization procedure described by Forman et al. (Forman et al., 1995). This procedure is based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate of 5% was applied to the statistical maps. Clusters reported here survived this control of multiple comparisons. The location of significantly activated clusters was assessed by superimposing the results from group analysis on an averaged brain using NeuroElf v0.9c.

To estimate the overall BOLD response for the task, the biological motion sequences were contrasted against the scrambled sequences. We also contrasted the BOLD responses for the trunk rotation and the manual transfer movements to evaluate the differences in somatotopic activation. In order to estimate the influence of the weight of the transferred object we conducted a conjunction analysis (Nichols, Brett, Andersson, Wager, & Poline, 2005) between the contrasts manual transfer 7 kg versus manual transfer 3.5 kg and trunk rotation 15 kg versus trunk rotation 7 kg.

3. Results

3.1. Performance data

The behavioral performance of all participants was poor. Eight subjects rated the higher weight higher than the lower weight on average over the 10 realizations for the trunk rotation movement and just 4 subjects over the 10 realizations for the manual transfer movement. Only two subjects rated the higher weight (marginally) higher than the lower weight in both movement conditions. Thus, the differences in the judgments of light versus heavy weights were close to guessing probability (Fig. 3). Consequently, we did neither find significant main effects for factors the weight ($F(1, 15) = 0.696$) and movement ($F(1, 15) = 0.243$) nor a significant interaction between factors the weight and movement ($F(1, 15) = 0.115$).

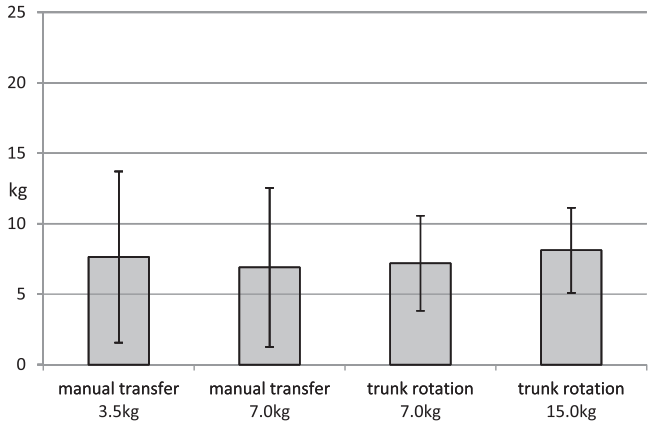

Fig. 3. Subjective weight ratings (mean and *SD*, in kg, $N = 16$) to manual transfer and trunk rotation movements.

3.2. Neuroimaging data

When comparing the activation while participants were watching point-light movements (manual transfer and trunk rotation) with the activation while scrambled light point stimuli were shown, we found significantly higher activation in a number of structures (Fig. 4, Table 1) including the primary visual cortex (V1), the fusiform gyrus bilaterally, the right superior temporal gyrus (STG), the primary sensory cortex (SI), the primary motor cortex (MI), the premotor cortex, the medial prefrontal cortex (mPFC), the left insula (INS), and the anterior cingulate cortex (ACC). There were cerebellar clusters in the right culmen and the left declive.

The scrambled movements evoked significantly higher BOLD activity in the left lentiform nucleus, the anterior end of the left STG, the middle frontal gyrus, the inferior parietal lobule (IPL), and the posterior cingulate (PCC).

Comparing the two kinds of movement, we observed extensive activations (Fig. 5, Table 2). For manual transfer versus trunk rotation these included activations in the precuneus, the middle and inferior temporal gyrus extending to the fusiform gyrus. There were parietal and dorsolateral prefrontal regions, as well as the hand and arm region of the MI (Talairach coordinates −43, 0, 24) and SI (Talairach coordinates −5, −51, 68; see Table 2).

For trunk rotation the activation was higher in the V1, the cuneus, the right middle temporal gyrus, the perigenual ACC, and the left anterior insula. Here too, there was an increased activity in SI (Talairach coordinates −7, −37, 70), although this did not survive the statistical correction. This activation was located in the back-region of somatosensory homunculus.

Consistent with the poor performance in the weight rating task, the conjunction of the contrasts manual transfer 7 kg versus manual transfer 3.5 kg and trunk rotation 15 kg versus trunk rotation 7 kg did not reveal any significantly activated clusters throughout the whole brain at an uncorrected cluster threshold of $p > .01$.

Finally, we analyzed the signal change in the ACC over the time course of our experimental blocks to investigate whether the activity is related to biological motion. In all conditions, the BOLD activity reached its maximum during the second presentation of the action sequence (Fig. 6). Activity returned almost to baseline by the beginning of the response period (Fig. 6).

4. Discussion

When judging the weight that is manipulated in visually displayed point-light stimuli, healthy participants show BOLD activity in the anterior cingulate, the insula, as well as in the somatosensory cortex and the cerebellum. The contrast of activation between manual transfer and trunk rotation

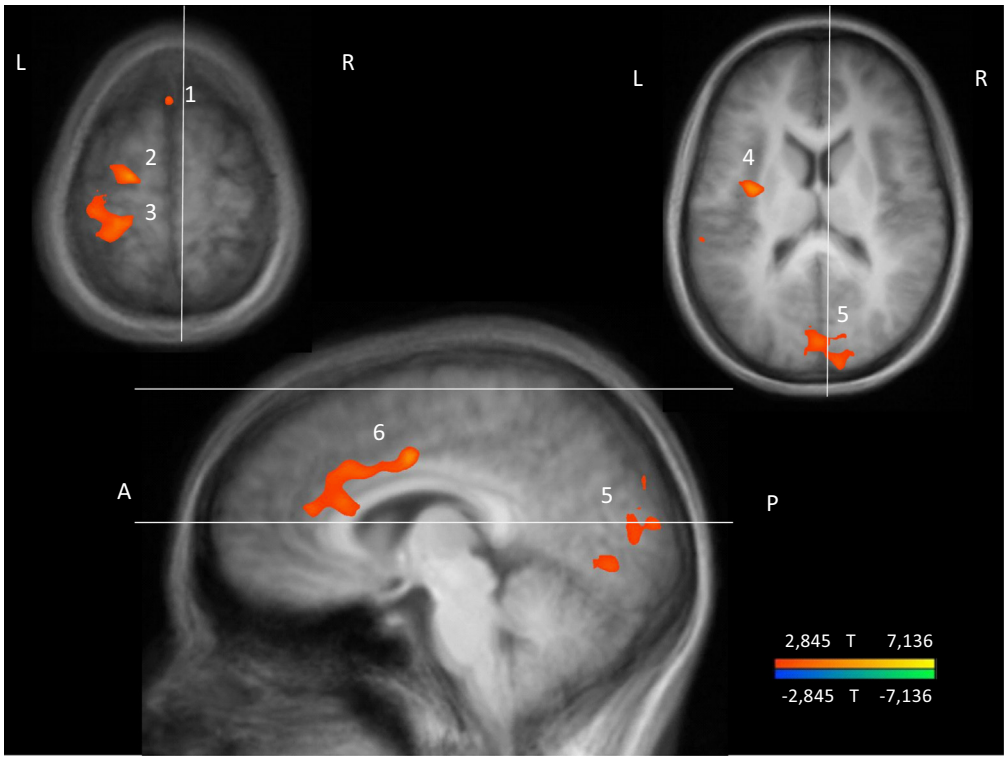

Fig. 4. Comparison of activations between movement and scrambled dots. The figure indicates that there are activations for movement (manual transfer and trunk rotation) vs. scrambled dots. Significant activations are rendered onto slices of an averaged T1 weighted brain image of all participants. The statistical threshold was $p > .05$ (cluster-corrected, 23 adjacent voxels). 1, medial prefrontal cortex; 2, premotor cortex; 3,SI/ MI; 4, insula; 5, cuneus; 6, ACC; Talairach coordinates: left: Z = 64, middle: X = 7, right: Z = 16.

movement shows a clear somatotopy in the somatosensory region. Unexpectedly, none of the subjects was able to report differently to the different weights. Neither did we find weight-related differences in the BOLD activity.

4.1. Behavioral data

The lack of a behavioral effect was unexpected but consistent across subjects. Only two of the subjects rated the heavier weights of both movement kinds as heavier than the lower weights, and even in these two subjects, the indicated differences were very small (less than the 1-kg steps on the response mask). The behavioral results were consistent with the conjunction analysis, which revealed no weight-related activities even at a non-corrected significance level.

The stimulus material was selected from a previous study where the healthy controls were well able to recognize the differences between the presented weights (de Lussanet et al., 2012), and similar to the stimuli used in other studies (de Lussanet et al., 2013; Runeson & Frykholm, 1981). We also tested the stimulus protocol of this experiment outside the scanner, and confirmed that subjects were able to recognize the weights. In one more control we found that subjects could discriminate between the weights when they were lying supine outside the scanner, and when they were explicitly instructed to remain still while body movements were recorded.

For the further discussion of our results it seems important to consider the lack of correct weight assessment. According to their verbal reports outside the scanner, the subjects did try to assess

Table 1
Increases in activation for movement compared to scrambled movement. For composite clusters, the local maxima (LM) are listed additionally.

X	Y	Z	Size of cluster	side	*t* value	Anatomical localization	BA
−8	−81	1	470	L	6.661	Lingual Gyrus	
						LM, Cuneus (−4, −77, −3; t = 5.83)	18
28	−40	−26	156	R	5.824	Culmen	
−38	−6	15	56	L	5.470	Insula	
3	18	33	351	R/L	5.287	Cingulate Gyrus	24
−1	21	51	24	R/L	5.151	Superior Frontal Gyrus	6
−19	−11	63	40	L	4.733	Middle Frontal Gyrus	6
−37	−77	−26	38	L	4.229	Declive	
−24	−32	65	62	L	3.917	Postcentral Gyrus	3
					3.895	LM, Postcentral Gyrus (−25, −38, 65; t = 3.896)	5
					3.829	LM, Precentral Gyrus (−35, −29, 64; t = 3.829)	4
49	5	−2	25	R	3.918	Superior temporal Gyrus	22
−38	−49	40	225	L	−3.877	Inferior Parietal Lobule	40
−34	10	−26	501	L	−4.276	Superior temporal Gyrus	38
−7	2	−6	714	L	−4.583	Sub-lobar, Extra-Nuclear, White Matter	
						LM, Lentiform Nucleus (−6, 3, −4; t = 3.981)	
−36	33	−12	237	L	−4.842	Middle Frontal Gyrus	11
44	−36	−6	759	R	−4.869	Temporal Lobe, Sub-Gyral, White Matter	
−14	−44	20	392	L	−4.930	Sub-lobar, Extra-Nuclear, White Matter	
						LM, Posterior Cingulate (−13,−50,−19; t = −3.375)	

All reported peaks passed a whole-brain cluster-threshold level of $p > .05$, and were required to be at least 23 connected voxels in volume. Coordinates refer to the Talairach space (Talairach & Tournoux, 1988). BA, Brodmann area; R, right hemisphere; L, left hemisphere; LM, local maximum.

properly. We therefore believe that the fMRI activations we found are necessary to be engaged in the weight lifting task, while they are not sufficient to perform this task correctly. Thus, we assume that the brain regions we found activated during the processing of biological motion stimuli are representative for the conduction of the weight rating task.

The lack of a behavioral effect was unexpected as healthy participants are usually able to perform cognitive tasks in the scanner. Moreover, in pilot experiments we found that subjects were able to judge the weights well, even when lying still in a supine position. A possible, though unspecific, explanation for the lack of weight recognition might be a generally higher arousal due to the conditions inside of the scanner. Another factor that might have made the judgments more difficult than in other studies (e.g., Runeson & Frykholm, 1981) is that the recording of the actions was timed with a metronome to ensure that the durations were the same. Although the same recordings have been used earlier, it might be that the combination of the arousal in the scanner and the relatively exact timing of the movements caused the lack of behavioral effects.

4.2. BOLD activity during weight lifting task versus scrambled dots

Assessment of biological motion stimuli was accompanied by extended activations in occipital, ventral temporal and middle temporal regions. These activations are expected and in line with the literature (Grèzes, Costes, & Decety, 1998; Grèzes et al., 2001; Lestou, Pollick, & Kourtzi, 2008; Michels, Kleiser, de Lussanet, Seitz, & Lappe, 2009; Muthukumaraswamy, Johnson, Gaetz, & Cheyne, 2006; Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005; Ptito, Faubert, Gjedde, & Kupers, 2003; Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001). These regions are usually considered as belonging to the typical visual processing routes in the brain.

Central to our research questions are pain-related brain regions that interfere with activations during the weight lifting task. Activated brain regions for biological motion were found in the frontal lobe and the postcentral part of the parietal lobe. The strictly somatotopic organization of the primary somatosensory cortex serves – among others – the discrimination of the potentially tissue-damaging sensory stimulation (Bushnell et al., 1999). Even when painful events are observed in others, S1

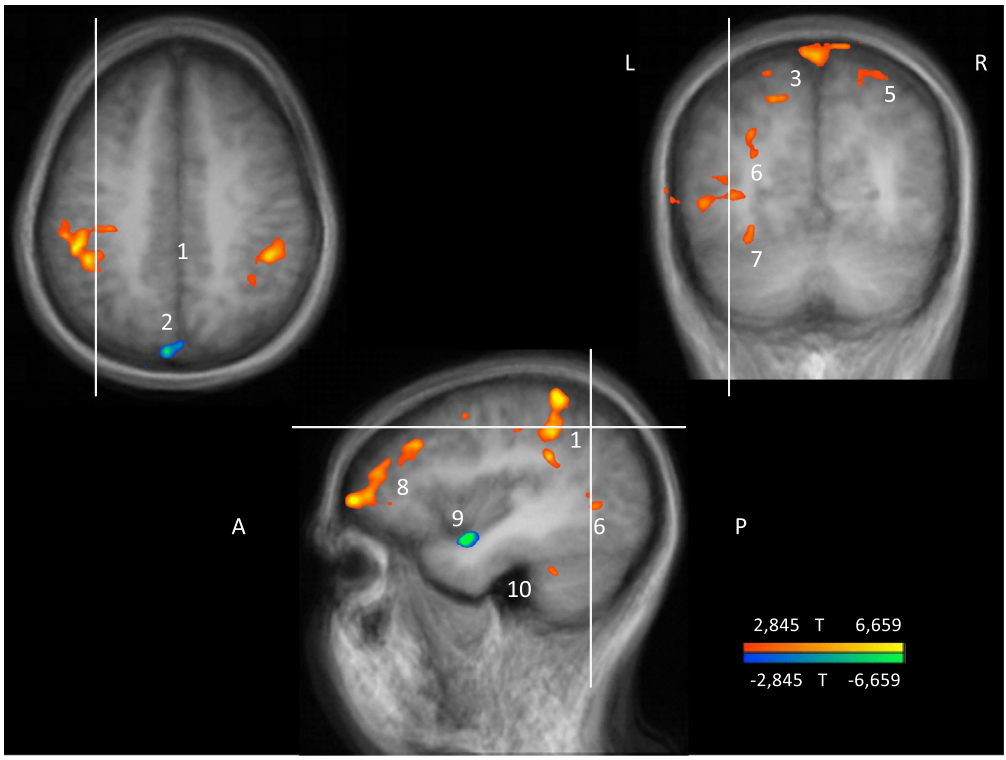

Fig. 5. Regions of significantly increased and decreased activations for manual transfer compared to trunk rotation movements. Significant activations are rendered onto slices of an averaged T1 weighted brain image of all participants. The statistical threshold was $p > .05$ (cluster-corrected, 27 adjacent voxels). 1, inferior parietal lobule (BA40), postcentral gyrus; 2, cuneus; 3, precuneus; 5, superior parietal lobule (BA7); 6, medial temporal gyrus; 7, fusiform gyrus; 8, medial frontal gyrus (BA6); 9, insula; 10, culmen; Talairach coordinates: left: Z = 43, middle: X = −38, right: Y = −59.

activity is modulated (Martinez-Jauand et al., 2012). Although the frontal lobe activity may not have a unitary role in pain processing, especially activity in prefrontal regions during painful stimulation is generally linked to attentional and cognitive processing of the painful event (Bornhovd et al., 2002; Tolle et al., 1999). Modulation of prefrontal cortex activity was also found during expectations subjects made about painful events (Wager et al., 2004).

Another region we found activated and that is typically involved in the processing of pain-related stimuli is the ACC. It is thought that the ACC plays a role in representing the affective nature of pain and painful stimuli (Vogt, 2005). One may ask whether seeing someone lifting a heavy object might be responsible for the ACC activity in our study. The ACC (and the MCC) are often found activated by biological motion stimuli, even when any emotion, conflict, or pain is avoided. Similar activity of ACC has been found in many studies, whether displayed as point-lights (Dayan et al., 2007; Grèzes et al., 1998, 2001; Lestou et al., 2008; Pelphrey et al., 2005; Ptito et al., 2003; Vaina et al., 2001), as stationary images (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006; Binkofski et al., 1999; Wheaton, Thompson, Syngeniotis, Abbott, & Puce, 2004), or as movies (Calvo-Merino, Glaser, Grèzes, Passingham, & Haggard, 2005; Corradi-Dell'Acqua, Tomasino, & Fink, 2009; Lausberg & Cruz, 2004; Muthukumaraswamy et al., 2006; Salomon, Malach, & Lamy, 2009). Since only one of these studies showed transitive stimuli (Lestou et al., 2008) it seems highly unlikely that the ACC activity in our study is solely due to the presentation and judgment of the handled weight. This interpretation is supported by the time course of the BOLD signals (Fig. 6). For all four kinds of stimulus blocks, the BOLD response in the ACC region rose during the presentation of biological motion, reaching a maximum

Table 2
Increases and decreases in activation for manual transfer compared to trunk rotation movement. For composite clusters, the local maxima (LM) are listed additionally.

X	Y	Z	Size of cluster	side	*t* value	Anatomical localization	BA
−34	−73	19	58	L	7.643	Middle Occipital Gyrus	19
27	−71	50	197	R	6.623	Precuneus	7
−43	48	4	44	L	6.208	Middle Frontal Gyrus	46
−36	−47	22	679	L	6.069	Superior Temporal Gyrus	13
−29	−58	30	51	L	5.980	Middle Temporal Gyrus	39
53	31	16	121	R	5.800	Inferior Frontal Gyrus	46
				R		LM, Middle Frontal Gyrus (50,35,17; t = 5.537)	46
−5	−51	68	158	L	5.673	Postcentral Gyrus	7
30	−94	9	111	R	5.472	Middle Occipital Gyrus	18
19	−3	55	110	R	5.351	Medial Frontal Gyrus	6
−60	4	−4	48	L	5.271	Superior Temporal Gyrus	22
−60	−63	0	56	L	4.916	Inferior Temporal Gyrus	37
47	−34	47	90	R	4.838	Inferior Parietal Lobule	40
15	17	31	62	R	4.567	Anterior Cingulate	
−43	0	24	39	L	4.447	Precentral Gyrus	6
−21	−96	2	37	L	4.407	Middle Occipital Gyrus	18
−32	−58	−18	39	L	4.300	Declive	
−49	−70	7	235	L	4.254	Middle Temporal Gyrus	39
49	7	26	40	R	4.253	Inferior Frontal Gyrus	9
−18	−58	42	63	L	4.162	Precuneus	7
−20	−59	60	98	L	4.080	Precuneus	7
30	−57	34	44	R	4.003	Angular Gyrus	39
−30	1	48	40	L	3.939	Middle Frontal Gyrus	6
−3	−73	−11	30	L/R	3.798	Declive	
−11	−86	−4	64	L	−4.223	Lingual Gyrus	17
13	34	−1	71	R	−4.619	Medial Frontal Gyrus	10
				R		LM, Anterior Cingulate (11,37,−5; t = 4.418)	
−6	−82	37	98	L	−4.796	Cuneus	
−15	61	−1	27	L	−4.863	Superior Frontal Gyrus	10
2	−83	16	183	L/R	−4.868	Cuneus	
63	−27	−11	77	R	−5.199	Middle Temporal Gyrus	31
14	14	60	28	R	−5.736	Middle Frontal Gyrus	6
−40	0	−13	52	L	−6.246	Insula	

All reported peaks passed a whole-brain cluster-threshold level of $p > .05$, and were required to be at least 27 connected voxels in volume. Coordinates refer to the Talairach space (Talairach & Tournoux, 1988). BA, Brodmann area; R, right hemisphere; L, left hemisphere, LM, local maximum.

well before the end of the biological motion stimuli and returned to baseline by the beginning of the response period.

In fact, the above incomplete list of studies shows hardly any general correspondences, other than that the presented material contained human actions or implied actions. For example, the tasks were very different, and these stimuli sometimes showed the whole body but in many studies only one part of the body, such as a hand, mouth or foot. Since the grey matter volume of the OCC in macaque monkeys depends strongly on the size of their social network (Sallet et al., 2011), one might expect that the human ACC always becomes active when human activities are observed.

We also found an activation of the insula during the weight lifting task. BOLD activity in the insular cortex is reported frequently in studies on the perception and recognition of biological motion (Saygin et al., 2004). Thus, our finding is in line with the literature.

There was no higher BOLD activity for biological motion in the posterior STS. However, the STS is found activated only in little more than half of the studies of biological motion (Grèzes et al., 2001). Remarkably, studies in which the subjects had a task that was specifically related to the biological motion STS showed less activity than scrambled motion (Peuskens, Vanrie, Verfaillie, & Orban, 2005; Porat, Pertzov, & Zohary, 2011; Yamamoto, Someya, Troje, Ogawa, & Watanabe, 2009).

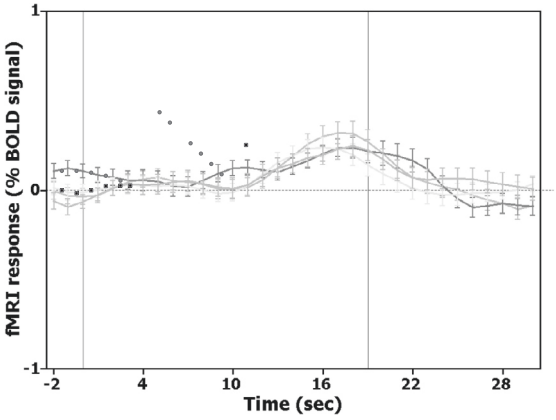

Fig. 6. Time course of the BOLD responses in the ACC during the presentation of the biological motion stimuli (trunk rotation 7.0kg, manual transfer 7.0kg, manual transfer 3,5kg, trunk rotation 15kg) and the response period. Time = 0: beginning of the first movie. Vertical line: end of the biological motion stimulus. The response period was variable (RANGE).

Overall, we found a generally higher activation for biological motion sequences as compared to scrambled motion. This higher activation is also not surprising. One reason for the higher activation might be the higher saliency of biological stimuli over unstructured stimuli. Biological motion stimuli can be expected to have received higher saliency due to their task-relevance (Taylor, Seminowicz, & Davis, 2009).

4.3. BOLD activity for manual transfer versus trunk rotation

Comparing the BOLD activity between both movement conditions, we found a clear somatotopy in the somatosensory regions. A somatotopy has been found in an fMRI study of mouth, hand, and foot actions, respectively, with static images as stimuli (Buccino et al., 2001).

In the present study, the manual transfer evoked a pronounced increase of BOLD activity in the hand and arm area of SI. The weight of the dumbbell in the manual transfer movements was half of that of the box in the trunk rotation movements. Therefore the load on each hand of the displayed actors was the same on average for the manual transfer and the trunk rotation movements. However, the stabilizing of the dumbbell and the transfer to the other hand requires much more manual control than the manipulation of a box hold in both hands (as in the manual transfer movement). Thus, it was expected that the manual transfer movements should evoke a higher BOLD activity in the hand and arm region of SI than the trunk rotation movement.

Conversely, the trunk rotation evoked a higher BOLD response in the trunk and back region of SI, although this activity did not survive the correction for multiple comparisons. The latter activity was expected, because the trunk rotation involves loading, movement, and fine coordination of the low back. In the manual transfer movement, on the other hand, the back remained motionless and unloaded.

The higher activations for the manual transfer movement as compared to the trunk rotation movement in frontal and mediotemporal areas were not expected. The duration of the sequences was the same, but the average velocity of the dots was about three times higher for the manual transfer movements than for the trunk rotation movements, even if the overall amount of movements of the dots is nearly identical. The higher average velocity of the point-lights might explain the increased BOLD activity in motion selective areas such as the mediotemporal gyrus.

4.4. Weight lifting task with respect to results in chronic low back pain

Our results, especially the activations in the primary and secondary somatosensory cortex (S1, S2), the anterior cingulate cortex (ACC), and the insula (INS), are of considerable interest with respect to

previous findings in chronic pain patients while viewing similar point-light motion stimuli (de Lussanet et al., 2013). It has been shown that chronic pain in a body part interferes with the ability to discriminate the manipulated weight when the manipulation involves movements of the painful body part, but not for other movements not involving that body part (de Lussanet et al., 2012). Additionally, the amount of handling usually helps healthy subjects to better judge the weight, while this is not the case in pain patients. In contrast, more handling interferes more strongly in chronic pain patients (de Lussanet et al., 2013). The results presented here offer a possible explanation for the impairment of weight judgment in pain patients. On the one hand, we demonstrated that the judgment of manipulated weights from point-light biological motion is associated with the activation of S1, S2, ACC, and INS. On the other hand, there are numerous studies demonstrating the involvement of the same structures during the processing of noxious stimuli and pain (e.g., (Apkarian et al., 2005; Peyron, Laurent, & Garcia-Larrea, 2000; Weiss et al., 2008). SI and SII are thought to be involved in the processing of the somatosensory component of pain, while ACC and INS have been associated with the analysis of the emotional component of pain (Rainville, Roy, Piche, Chen, & Peretz, 2009; Tracey & Mantyh, 2007; Treede, Kenshalo, Gracely, & Jones, 1999) as well as saliency (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Liang, Mouraux, & Iannetti, 2013). So it might be possible that the impaired judgment of manipulated weights in point-light motion stimuli in chronic pain patients results from an interference between of processing to judge weights and the processing of pain in one or several of these regions, i.e., SI, SII, ACC, and/or INS. More precisely, given that the impairment was found only for point-light biological motion that involves the affected body part, but not for movements of other body parts, it is more likely that the interference occurs at the level of SI or SII, even when we cannot exclude ACC and INS definitely due to the homuncular organization of parts of these structures (Baumgartner, Vogel, Ohara, Treede, & Lenz, 2011).

4.5. Limitations and future directions

An unfortunate result of the present study was the finding that none of the subjects was able to perceive the differences in the manipulated weight, and correspondingly, the lack of weight-related differences in the BOLD responses. For this reason it is advisable to choose a different task for fMRI experiments. Moreover, this study would have benefited by another baseline condition in which point light-actors are shown that do not lift any weight. This would assure the specifity to the contrasted action more precisely than the scrambled conditions used in the present work.

Still, given that the different stimuli activated somatosensory regions in a somatotopic manner provides future possibilities for studying the changes in motor representations due to chronic pain in corresponding patient groups.

5. Conclusion

In summary, the investigation of point-light biological motion for two types of movements performed with different weights demonstrated strong activation of primary and secondary somatosensory regions, the anterior cingulate cortex, and the insula in healthy subjects. Probably, the activation of the somatosensory regions serves the judgment of weight information from the biological motion stimuli, while the activation of the anterior cingulate and the insula probably serves the integration of behaviorally relevant information. These findings provide important information for the understanding of mechanisms underlying the judgment task, but possibly also why chronic pain patients are impaired in this task. Finally, the somatotopic organization in the contrast of the two activities confirms earlier findings that different sensorimotor networks are recruited depending in the exact action that is visually presented.

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Human brain stem structures respond differentially to noxious heat

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Concerning the physiological correlates of pain, the brain stem is considered to be one core region that is activated by noxious input. In animal studies, different slopes of skin heating (SSH) with noxious heat led to activation in different columns of the midbrain periaqueductal gray (PAG). The present study aimed at finding a method for differentiating structures in PAG and other brain stem structures, which are associated with different qualities of pain in humans according to the structures that were associated with different behavioral significances to noxious thermal stimulation in animals. Brain activity was studied by functional MRI in healthy subjects in response to steep and shallow SSH with noxious heat. We found differential activation to different SSH in the PAG and the rostral ventromedial medulla (RVM). In a second experiment, we demonstrate that the different SSH were associated with different pain qualities. Our experiments provide evidence that brainstem structures, i.e., the PAG and the RVM, become differentially activated by different SSH. Therefore, different SSH can be utilized when brain stem structures are investigated and when it is aimed to activate these structures differentially. Moreover, percepts of first pain were elicited by shallow SSH whereas percepts of second pain were elicited by steep SSH. The stronger activation of these brain stem structures to SSH, eliciting percepts of second vs. first pain, might be of relevance for activating different coping strategies in response to the noxious input with the two types of SSH.

Keywords: A-delta fiber, C-fiber, second pain, pain descriptors, PAG, RVM, periaqueductal grey, rostral ventromedial medulla

INTRODUCTION

Nociceptive stimulation evokes activity in a number of brain structures including the brain stem. Thereby differential nociceptive stimulation in animals leads to differential activity in the brain stem. Studies in rats indicate that brain stem structures related to nociception like the periaqueductal gray (PAG) and the nucleus Raphe magnus (NRM) in the rostral ventromedial medulla (RVM), are activated differentially by different slopes of skin heating (SSH) (Lumb et al., 2002; Lu et al., 2004; Parry et al., 2008). So the dorsolateral PAG was shown to be preferentially activated in response to steep SSH while activation of the ventrolateral PAG was observed preferentially to shallow SSH (Lumb et al., 2002; Parry et al., 2008). Furthermore, Lu et al. (2004) revealed in rats that activation of the NRM (and nocifensive effects) were different for steep vs. shallow SSH.

Moreover, brain stem activity is directly associated with modulation of pain intensity. So, electrical stimulation of the PAG, one of the brain stem areas usually activated by nociceptive input, has been shown to produce analgesia (Basbaum and Fields, 1984). In animals, distinct brain stem structures have been shown to be associated with distinct behavioral and cardiovascular components of nociceptive reaction. In humans, studies already revealed the importance of brain stem structures for the modulation of pain (Bromm and Treede, 1987b; Behbehani, 1995; Bandler et al., 2000). Recently, placebo analgesia was directly associated with the activity of PAG and RVM (Eippert et al., 2009). This might be of clinical importance because a specific activation of the brain stem could be associated with a reduction of pain perception. Such a pain-modulation would be interesting especially for chronic pain patients.

Taking into account the above-mentioned activations of PAG and RVM in response to different SSH in animals, we aimed to investigate brain stem activation to two different SSH in humans. However, the paradigm used in animals is difficult to realize in human due to at least two reasons: first, nociceptive stimulation in animals was realized with temperatures up to 60°C for a longer period of time. Such stimulation would cause serious injury in humans (Lumb, 2002; Lu et al., 2004). Second, there were single heat ramps with a delay of 8 min between two stimulations in the animal experiments. This delay is too long even for a block design in functional MRI (fMRI). To our knowledge, there are no studies using different SSH in humans to investigate brain stem activation. However, there are human studies using trains of thermal stimuli with different frequencies (Price et al., 1977; Staud et al., 2007). In these studies, trains of thermal stimuli with different intervals between noxious heat stimulations were applied. Modulating frequency of heat stimulation, humans reported different pain percepts (Price et al., 1977; Price, 1988; Staud et al., 2007) that might be assigned to two distinct conceptual entities, i.e., "first pain" and "second pain." The so called "first pain" can be clearly localized, feels pricking, and occurs fast and first after nociceptive stimulation (Bromm and Treede, 1987a; Magerl et al.,

1999; Beissner et al., 2010). First pain is considered to inform the individual about the location of an injury at and within the body and about the sensory quality of the injury. The so called "second pain" can less clearly be localized. Second pain is described as dull or pressing and occurs later after nociceptive stimulation than first pain (Price, 1988; Miltner, 1989; Magerl et al., 1999; Beissner et al., 2010). The prolonged second pain is considered to pull the individuals attention to the injury and to convey information to the brain that provides the basis for pain-related affect, arousal, and behavioral responses to limit further injury and to optimize recovery. Concerning the two types of pain, it has been shown that second pain is enhanced and first pain is suppressed when moderately painful heat is presented with a frequency of greater than 0.3 Hz (Price et al., 1977; Staud et al., 2007). When painful heat is presented with frequencies below 0.17 Hz, first pain is not suppressed and no enhancement of second pain occurs (Price et al., 1977; Staud et al., 2007). This is in line with Bromm's and Treede's suggestion (Bromm and Treede, 1987a) that second pain is perceived when first pain is reduced and vice versa.

In humans, different SSH have not been investigated to evoke different activation in brain stem structures so far. With the first (fMRI) experiment, we aimed at finding a method to test whether noxious heat stimulations with different SSH does activate brain stem structures differentially. According to animal studies, we expect a differential activation of PAG and RVM to different SSH. With the second experiment, we tested whether the different SSH used in the fMRI environment are associated with different pain qualities as stimulation with different SSH were associated with different behavioral responses in animal studies (Lumb, 2002).

MATERIALS AND METHODS

We conducted two experiments, one inside and one outside the fMRI scanner. Both experiments used the same thermal stimulation with steep and shallow SSH. Subjects were informed about the procedure and provided written informed consent. To familiarize the participants with the experimental procedure and the stimulus types, each subject received a brief demonstration of the thermal stimulation prior to the experiment. Participants were otherwise naive about the purpose of the experiments. No subject had any history of neurological, psychiatric, or pain disorder. They were free to withdraw from the experiment at any time. The procedure was approved by the local ethics committee of the Friedrich Schiller University of Jena.

DETERMINATION OF THE PAIN SENSITIVITY

Thermal stimuli were applied by a fMRI-compatible Peltier thermode (Medoc Advanced Medical systems; Ramat Yishai, Israel). The thermode had a surface area of 9 cm^2. Subjects were instructed to rate a series of thermal stimuli applied to the thenar eminence of their left hand using a modified Ellermeier scale (Ellermeier et al., 1991). This scale starts with 0 for "no pain" with an open scale with verbal description 1–10 = "just perceived," 11–20 = "clearly perceived but not painful," 21–30 = "very slightly painful," 31–40 = "slightly painful," 41–50 = "medium pain," 51–60 = "strong pain," 61–70 = "very strong pain." It was explained that pain should be rated with values higher than 70 if pain becomes worse. The original Ellermeier scale has good psychophysical properties (Ellermeier et al., 1991). We included 20 additional steps at the lower end to represent non-painful perceptions. Subjects were instructed to make a judgment regarding the categories first and subsequently rate the pain intensity within the range defined by this category. The rating requested was just the discrete number of rating that was monitored for further analysis.

To determine the pain sensitivity, thermode temperature was increased to a maximal stimulation temperature of 44°C–49°C in steps of 1°C. The procedure was as follows: a starting temperature of 34°C was established. Then, one full ramp with rise and fall of 10°C (2.5°C/s) was applied providing a maximal temperature of 44°C. Subject's intensity rating was recorded. The next starting temperature with a step of 1°C was established (up to a maximum of 39°C), followed by the next ramp with similar parameters (increase of 10°C with 2.5°C/s rise and fall). The procedure was finished at either 49°C maximal temperature or before maximal temperature of 49°C when subjects reported a rating of 51 or higher on the scale described above. This procedure allows the fitting of a stimulus-response curve presenting subjective ratings in dependence of the maximal temperature used for stimulation. It also familiarized the subjects with the kind of stimulation of the main experiments. For the succeeding main experiments, a T_{hot} was determined as the temperature where the subject reported a value of 50 on our modified Ellermeier scale. T_{hot} of all participants varied between 46.5°C and 49°C. Another maximal temperature of stimulation was used (T_{warm} = 40°C) providing ratings in the range below 20 on our scale.

THERMAL STIMULATION

Trains of thermal stimuli with different SSH are used for the experiments. This is an ecologically valid procedure to induce pain percepts. Thermal stimuli were applied to the thenar eminence of the right hand. Subject received two different types of heat pulse trains (steep vs. shallow SSH) applied with two different temperature levels (T_{hot} vs. T_{warm}). Heat pulse trains were balanced to control for order effects.

A design with four conditions was used, steep SSH with T_{warm}, steep SSH with T_{hot}, shallow SSH with T_{warm}, and shallow SSH with T_{hot} (**Figure 1**). The four conditions were presented in stimulation blocks. Five stimulation blocks containing one of each condition were presented throughout the whole experiment (**Figure 1**). Within a stimulation block, a baseline of at least 20 s (see below) was introduced between conditions (**Figure 1**). Each condition consisted of five heating ramps of identical type. During *WARM* conditions, temperature rose to 40°C (T_{warm}), whereas in the *HOT* conditions temperatures rose to T_{hot}. The baseline temperature before stimulation was set to 10°C below T_{warm}/T_{hot} and rose to these target temperatures with two different slopes: *steep SSH* runs had a slope of 7.5°C/s and *shallow SSH* runs had a slope of 2.5°C/s (**Figure 1**). Thus, painful heat peaks of the steep SSH stimuli were applied with a frequency of 0.3 Hz, whereas painful heat peaks of the stimuli with shallow SSH were applied with a frequency of 0.17 Hz in the *HOT* conditions. There was a baseline interval between stimulation blocks of 30 s.

A 30 s time interval with a constant baseline temperature (10°C below T_{warm} in the *WARM* and 10°C below T_{hot} in the *HOT* conditions) was introduced between the steep and the shallow SSH

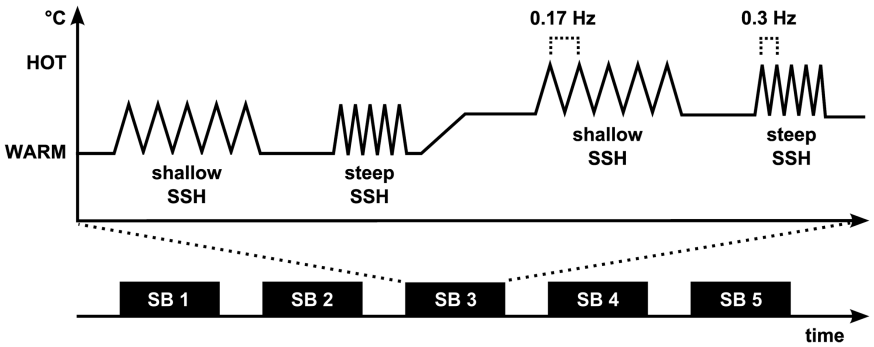

FIGURE 1 | Experimental paradigm. The fMRI experiment (Experiment 1) consisted of five stimulation blocks (SB). Each of the four stimulation conditions was presented once during each SB. Painful heat peaks of the steep SSH stimuli were applied with a frequency of 0.3 Hz whereas painful heat peaks of the stimuli with shallow SSH were applied with a frequency of 0.17 Hz. During Experiment 2, shallow and steep SSH were applied only for the hot temperature.

conditions of each temperature. The baseline temperature rose over the course of 20 s from 10°C below T_{warm} to 10°C below T_{hot} for a change in stimulation from *WARM* to a succeeding *HOT* condition, or decreased from 10°C below T_{hot} to 10°C below T_{warm} for a change in the stimulation from *HOT* to a succeeding *WARM* condition, respectively (**Figure 1**). This temperature was kept for another 20 s before the next heating ramps began. The sample was split concerning the order of shallow and steep SSH heating to control for order effects of conditions.

Experiment 1

Experiment 1 investigated the activation of the brainstem by means of fMRI for the different SSHs.

Sixteen healthy, right-handed subjects (seven male, nine female, 19–28 years) volunteered in the fMRI experiment. Subjects were paid €12 for completing the experiment. Prior to the experiment, the stimulus-response function to thermal stimulation of the subjects was examined as outlined above.

FUNCTIONAL IMAGE ACQUISITION

Scanning was performed with a 3T magnetic resonance scanner (Tim Trio, Siemens Medical Systems, Erlangen, Germany). The experiment started with a high-resolution T1-weighted scan of the brain (192 slices, TE = 5 ms, FOV: 256 mm × 256 mm, resolution: 1 mm × 1 mm × 1 mm) for anatomical referencing and visualization. A shimming procedure preceded the succeeding functional MR scanning. The first four volumes were discarded in order to improve field homogeneity. In the experimental fMRI run, 650 volumes were acquired using a T2* weighted echo-planar sequence (TE = 75 ms, TR = 1.8 s; FOV = 192 mm × 192 mm). Each volume comprised 24 slices (2 mm thickness and 2 mm × 2 mm in-plane resolution) (see **Figure A1** in Appendix) which were prescribed parallel to the brainstem. The FOV covered the *a priori*-defined region of interest which was centered around the PAG and enclosed the upper brainstem and the midbrain (**Figures 2B**, **A1** in Appendix).

fMRI PREPROCESSING

Preprocessing and analysis of fMRI data was performed using BrainVoyagerQX 2.1 (Brain Innovation, Maastricht, Netherlands). Primarily, all volumes were realigned to the first volume in order to minimize effects of head movements on data analysis. Further data preprocessing comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) and temporal smoothing (high pass filter: 15 cycles per run; low pass filter: 2.8 s; linear trend removal). The anatomical and functional images were co-registered (**Figure A2** in Appendix) and normalized to the Talairach space (Talairach and Tournoux, 1988).

fMRI STATISTICAL ANALYSIS

Statistical analyses were performed by multiple linear regression of the signal time course at each voxel. The expected blood oxygen-level-dependent (BOLD) signal change for each of the four conditions (predictors) was modeled by a canonical hemodynamic response function. A random-effects General Linear Model was used to identify associated brain activity in all acquired slices. To minimize false-positive results (Straube et al., 2008) we tested whether the detected clusters survived a correction for multiple comparisons. We used the approach as implemented in Brain Voyager (Goebel et al., 2006), which is based on a 3D extension of the randomization procedure described by Forman et al. (1995). This procedure is based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate of 5% was applied to the statistical maps. Clusters reported here survived this control of multiple comparisons. For subsequent visualization of activated brain regions, the location of significantly activated regions was assessed by superimposing the results from group analysis on an averaged brain.

As the intent of this study was to characterize the changes in blood oxygen level dependent (BOLD) response to the painful stimulation, we compared the two different SSHs in the *HOT* conditions. The brain stem clusters found for this contrast constitute the basis for the analysis of further effects. The coordinates of the peak voxels were allocated to the anatomical structures with the assistance of an atlas of the human brain stem (Paxinos and Huang, 1995). For this comparison we also conducted repeated measures *t*-tests for the peak voxel of each structure.

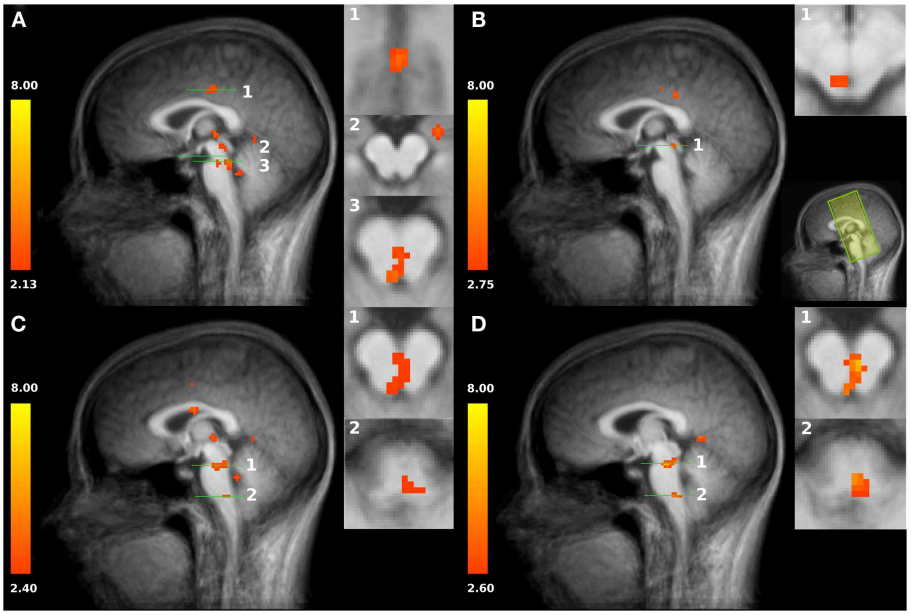

FIGURE 2 | (A) Increased activation of both *HOT* conditions compared to baseline in the posterior cingulate cortex PCC (slice plane 1), amygdala (slice plane 2), and PAG/NRD (slice plane 3). **(B)** Increased activation to shallow SSH compared to baseline in superior part of the PAG (slice plane 1); Field of view (FOV) with coronal slices **(C)** Increased activation to steep SSH compared to baseline in inferior part of the PAG, NRD (slice plane 1), and RVM (slice plane 2). **(D)** Increased activation to steep SSH compared to shallow SSH in PAG, NRD (slice plane 1), and RVM (slice plane 2). Statistical parametric maps are overlaid on a T1 scan (neurological convention, left = left).

Additionally, conditions we used repeated measures ANOVAs to assess the differential effects of the four conditions.

Experiment 2

Experiment 2 was conducted to prove whether the different SSH are able to elicit different pain percepts. This is an important question with respect to the discussion concerning different types of afferents possibly involved during this type of stimulation.

Prior to the experiment, the stimulus-response function of the subjects was assessed analogously to Experiment 1. Stimuli with different SSH were then applied similarly to Experiment 1 with two exceptions: first, there was no *WARM* condition included. Second, the *HOT* condition was presented 10 times (5 times with steep and 5 times with shallow SSH). Directly after each *HOT* condition, subjects were requested to indicate how the stimuli of different SSHs were perceived. We used a (restricted) three-item verbal descriptor list which has been shown that it can reliably indicate whether the pain sensation evoked by the physical stimulus is the result of predominantly Aδ (first pain) or C-fiber activity (second pain) (Beissner et al., 2010). According to Beissner et al. (2010), "pricking" is an indicator for the first pain, while "pressing" or "dull" are indicators for the second pain. Thus, subjects were requested to choose the appropriate perception(s) from this list of three adjectives for the previous stimulation.

Twenty-three healthy right-handed subjects (3 male, 20 female, 19–28 years) volunteered in Experiment 2. Subjects were paid €5 for completing the experiment.

For the analysis of the data of Experiment 2, odds ratios (OR) were calculated separately for each of the three descriptors according to Beissner et al. (2010) as (A·D)/(B·C). The capital letters have the following meaning:

A: number of selections of the given descriptor for stimulations with steep SSH;
B: total number of stimulations with steep SSH minus A (i.e., the number of selections of the given descriptor for stimulations with steep SSH);
C: number of selection of the given descriptor for stimulations with shallow SSH;
D: total number of stimulations with shallow SSH minus C (i.e., number of selection of the given descriptor for stimulations with shallow SSH).

If "pricking" will be chosen more often for shallow SSH ($OR < 1$), then we might conclude that this stimulation preferentially activates Aδ-fibers. Accordingly, if "pressing" and/or "dull" will be chosen more often for steep SSH ($OR > 1$), then we might conclude that this stimulation preferentially activates C-fibers. Ninety-five percent confidence intervals, calculated as $OR \pm 1.96 \cdot (1/A + 1/B + 1/C + 1/D)^{0.5}$, were utilized to evaluate the significance of the respective ORs.

RESULTS

EXPERIMENT 1

First, we tested whether brain stem regions show activation during the noxious thermal stimulation compared to baseline. We found activation to both SSH in the painful *HOT* conditions compared to baseline in an inferior part of the PAG, probably including

nucleus Raphe dorsalis (NRD) according to (Paxinos and Huang, 1995) [$t(15) = 3.354$, $p < 0.005$, *x*, *y*, *z*: 0, −29, −20] (**Figure 2A**, No. 3). More specifically, stimulation with shallow SSHs (vs. baseline) led to higher activation in a more superior part of the PAG [$t(15) = 3.24$, $p < 0.01$, *x*, *y*, *z*: −3, −28, −6, **Figure 2B**], whereas the stimulation with the steep SSHs yielded higher activation in the PAG/NRD complex [$t(15) = 3.77$, $p < 0.005$, *x*, *y*, *z*: 1, −25, −19, **Figure 2C**]. Furthermore, the steep SSHs in the T_{hot} condition showed activation in a brain stem cluster that probably represents the RVM according to (Paxinos and Huang, 1995) [$t(15) = 3.12$, $p < 0.01$, *x*, *y*, *z*: 3, −33,−43, **Figure 2C**]. More importantly, we investigated whether these brain stem regions show differential responses under the two painful experimental conditions (*HOT*), i.e., with steep vs. shallow SSHs. This contrast revealed significantly stronger activation in the inferior part of the PAG [$t(15) = 3.54$, $p < 0.005$, 16 voxel, *x*, *y*, *z*: 1, 31, 17], NRD [$t(15) = 4.93$, $p < 0.001$, 40 voxel, *x*, *y*, *z*: 2, 25, 18], and RVM [$t(15) = 3.82$, $p < 0.005$, 16 voxel, *x*, *y*, *z*: 2, 30, 42]. No significant differences were found for the comparison between steep and shallow SSH in the *WARM* conditions (PAG [$t(15) = 0.18$, $p > 0.1$], NRD [$t(15) = 1.57$, $p > 0.1$], and RVM [$t(15) = 0.53$, $p > 0.1$]). The clusters of higher activation to steep vs. shallow SSHs are shown in **Figure 2D**; β-values of BOLD responses are shown in **Figure 3**. In contrast to the higher activation observed for steep SSHs, we did not find any statistically significant difference for the comparison shallow SSHs vs. steep SSHs for T_{hot}.

Repeated measures ANOVAs for main effects and interactions of all other conditions were performed for β-values of peak voxels where significant effects were found for the contrast of interest, i.e., steep vs. shallow SSH in the *HOT* condition. ANOVA revealed a main effect of temperature for the NRD cluster with stronger activation for T_{hot}, a main effect of type of SSH in PAG with stronger activation for steep SSH, and an interaction for temperature × SSH in the NRD (**Table 1**). The significant interaction term for the NRD was investigated with a contrast analysis. There is a higher activation for steep SSH vs. shallow SSH in the *HOT* condition [$t(15) = 4.932$, $p < 0.001$], but no significant difference in activation between steep and shallow SSH in the *WARM* condition. Conversely, we found a higher activation for steep SSH with T_{hot} as compared to with T_{warm} [$t(15) = 4{,}058$, $p = 0.001$] whereas no difference was found for the shallow SSH between T_{hot} and T_{warm}.

Second, we used our restricted field of view (remember that the acquired slices concentrated on brainstem activation and did not allow the mapping of the whole "neuromatrix of pain" (Treede et al., 1999; Tracey and Mantyh, 2007; Iannetti and Mouraux, 2010; Schweinhardt and Bushnell, 2010)) to prove our experimental manipulation. We found higher activations to both SSH in the painful T_{hot} conditions compared to baseline in the posterior cingulate cortex [PCC, $t(15) = 3.498$, $p < 0.005$, 252 voxel, *x*, *y*, *z*: 1, −19, 35; **Figure 2A**, No.1], in left amygdala [$t(15) = 3.44$, $p < 0.005$, 312 voxel, *x*, *y*, *z*: 21, −10, −12; **Figure 2A**, No. 2], and in the medial thalamus [$t(15) = 3.19$, $p < 0.01$, 40 voxel, *x*, *y*, *z*: −1, −22, 1; **Figure 2**]. These results indicate that our paradigm with different SSH is suitable to activate brain regions that have been found to process noxious thermal stimuli in other studies (Peyron et al., 2000).

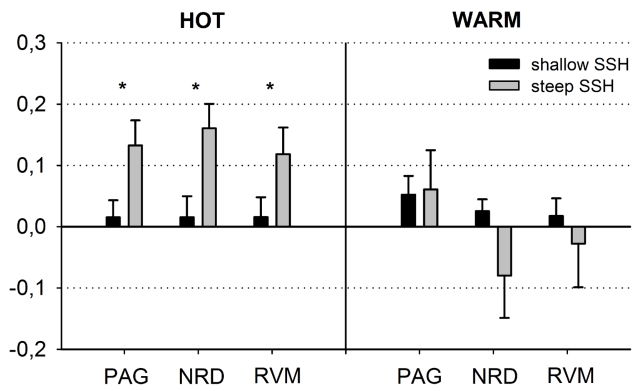

FIGURE 3 | Schematic overview of the blood oxygen level dependent (BOLD) responses in the periaqueductal gray (PAG), the nucleus Raphe dorsalis (NRD), and the rostral ventromedial medulla (RVM) (steep vs. shallow SSH for T_{hot} and T_{warm} conditions). The figure depicts means ± SE of parameter estimates for the peak voxel of the structures.

EXPERIMENT 2

Odds ratios (and 95% confidence intervals) were calculated separately for the three descriptors (**Figure 4**). Clearly, the descriptor "pricking" which is associated with first pain was chosen significantly more often for the stimulation with the shallow SSH, whereas the descriptor "dull" which is associated with second pain, was chosen significantly more often for the stimulus with the steep SSH. The descriptions for "pressing" did not reach a significant discrimination between the different SSH (**Figure 4**).

DISCUSSION

Using different SSH, our primary finding is a stronger BOLD activity in response to trains of painful heat stimuli with steep SSH as compared to trains of painful heat stimuli with shallow SSH. Higher activation was found in the inferior part of the PAG, probably including the NRD according to (Paxinos and Huang, 1995), and a cluster that probably represents the RVM according to (Paxinos and Huang, 1995). We did not find any stronger activation in the brain stem for the contrast shallow vs. steep SSH. Thus, this

Table 1 | Main effects and interactions of parameter estimates for the factors Temperature and SSH within the brain stem.

	Talairach *x, y, z*	Volume	Temperature	SSH	Temperature x SSH
PAG	1, −31, −17	16	$F(1, 15) = 0.203$, $p > 0.1$	$F(1, 15) = 5.607$, $p = 0.032$	$F(1, 15) = 2.977$, $p > 0.1$
NRD	−2, −25, −18	40	$F(1, 15) = 13.303$, $p = 0.002$	$F(1, 15) = 0.326$, $p > 0.1$	$F(1, 15) = 10.631$, $p = 0.005$
RVM	2, −30, −42	16	$F(1, 15) = 3.17$, $p = 0.095$	$F(1, 15) = 0.522$, $p > 0.1$	$F(1, 15) = 3.215$, $p = 0.0903$.

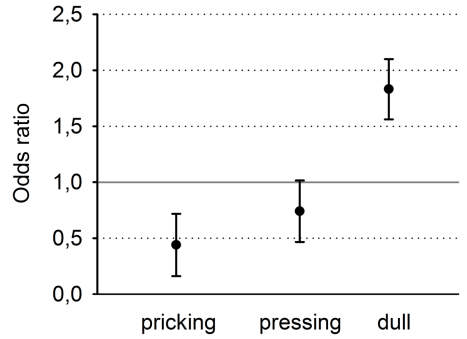

FIGURE 4 | Odds ratios and 95% confidence intervals of the three descriptors, sorted from left to right for increasing selectivity for second pain and decreasing selectivity for first pain.

method is able to differentially activate structures in the human brain stem. To our knowledge, this is the first time that differential activation to peripheral noxious stimulation is demonstrated in humans.

The stronger activation in the PAG/NRD complex and the RVM observed to steep vs. shallow SSH is surprising with respect to animal studies. In animal experiments, the shallow SSH, and not the steep SSH yielded more activation. Several reasons might account for this result. First, the maximal temperatures of stimulation differed between the present experiment (49°C) and the animal studies [e.g., 55°C (Lumb, 2002)]. It is well known that the characteristics of nociceptors differ in their response behavior for this temperature range (Behbehani, 1995). Second, the differences might be due to our spatial resolution. The resolution of brain scans with 2 mm × 2 mm × 2 mm in the present study might not have been sufficiently high to detect activations in different columns of the PAG. Third and probably most important, single ramps with shallow SSH were employed in the animal experiments. Such stimulation was shown to preferentially activate C-fibers, whereas single steep SSH are able to preferentially excite Aδ-fibers (Lumb, 2002; Lumb et al., 2002). In contrast to the animal experiments, a train of five succeeding heating ramps without gaps was employed in our study. Thereby, the steep SSH resulted in a frequency of heat peaks of 0.3 Hz. A stimulus frequency of 0.3 Hz is known to produce the phenomenon of temporal summation of second pain, i.e., TSSP (Price et al., 1977; Herrero et al., 2000). TSSP is considered to result from C-fiber evoked responses in dorsal horn neurons, termed "windup" (Herrero et al., 2000; Sarlani and Greenspan, 2005). Thus, the involved fibers activated by the steep SSH in animal studies are Aδ-fibers while the activation with repeated steep SSH in our experiment might preferentially involve C-fibers. Following this interpretation, the activation of the brain stem by steep SSH of stimulus trains in our study has to be compared to the single shallow SSH in the animal experiments. Considering this, both experiments yielded similar results.

The results of Experiment 2 are of crucial importance for the latter consideration. It investigated the quality of pain percepts that are elicited by different SSHs in humans. Indeed, we found evidence that the steep SSH was associated with the percept "dull" whereas the shallow SSH was associated with the percept "pricking." In accordance with Beissner et al. (2010), these descriptors distinguish best between first pain and second pain. Thus, steep SSH might be associated with a predominant activation of C-fibers while the shallow SSH might be associated with a predominant activation of Aδ-fibers. This interpretation is in line with other studies using trains of painful thermal stimuli that were associated with different pain percepts (Price et al., 1977; Staud et al., 2007). Characteristics of first pain were associated with a frequency of 0.17 Hz between the painful heat peaks whereas characteristics of second pain were associated with a frequency of 0.3 Hz between the painful heat peaks (Price et al., 1977; Staud et al., 2007). However, it should be mentioned that heat is perceived as painful in humans only at temperatures above 43°C (Julius and Basbaum, 2001). Thus, just the top of each heating ramp can be considered as a painful heat peak. In the present study, the painful heat peaks of the steep SSH stimuli were applied with a frequency of 0.3 Hz whereas heat peaks of the stimuli with shallow SSH were applied with a frequency of 0.17 Hz so that these ramps fulfill the frequency criterion for painful stimulation. Taking together the two experiments, we suggest that the different SSH probably activate different types of peripheral input resulting in different pain percepts (first vs. second pain).

We found activation of the PAG and the RVM to stimulation with noxious heat to both types of SSH. Several brain imaging studies have observed activations in brainstem structures to nociceptive stimulation (Apkarian et al., 2005; Tracey and Mantyh, 2007; Eippert et al., 2009; Schweinhardt and Bushnell, 2010). Brainstem modulation of neuronal activity in the spinal cord has been reported since more than a century ago (Bernard, 1858) and is thought being involved in top-down control of pain. In particular, the midline PAG integrates input from the spinal cord, cerebral cortex, and numerous other brainstem nuclei (Apkarian et al., 2005; Eippert et al., 2009). Its stimulation in humans was shown to result in antinociception and analgesia (Hosobuchi et al., 1977). In contrast, its lesion might result in chronic pain (Basbaum and Fields, 1984). Our result of an increased activity in the inferior part of the PAG in response to steep as compared to shallow SSH might, therefore, be an important result. Based on the animal studies mentioned above, this higher activation might indicate that the steep SSH stimulation, but not the shallow SSH stimulation might trigger the nocifensive part of PAG. Moreover, the hypothesis that this type of activation might result in an activation of nocifensive reaction might be tested and, if true, possibly be used for chronic pain patients.

We found a higher activation within the inferior part of the PAG to stimulation with steep as compared to shallow SSH. This result is in line with previous studies in animals. Animal studies have found different activation patterns within distinct columns of the PAG to preferential C- and Aδ-fiber stimulation (Lumb, 2002; Lumb et al., 2002; Parry et al., 2008). It has also been proposed that the different columns of the PAG not only differ with respect to the influence of the ongoing nociceptive information processing as outlined above, but also mediate different coping strategies (Lumb et al., 2002). Preferential Aδ-fiber stimulation is

associated with activation of dorsolateral and lateral columns of the PAG which in turn result in active coping strategies (Lumb et al., 2002). The activation of these columns evokes sympathetic excitation. Passive coping strategies are closely linked to the ventrolateral columns of the PAG activated by preferential C-fiber stimulation. The activity of the ventrolateral PAG is associated with sympathoinhibition (Lumb et al., 2002). Correspondingly, the PAG mediates differential control of spinal nociception as part of a defensive response or as withdrawal. It has been established to carry out integrative functions for cardiovascular and respiratory regulation, for sensory modulation, and for different motor behaviors (Clement et al., 2000; Morgan and Carrive, 2001; Subramanian et al., 2008; Heinricher et al., 2009). Reflecting these results on our data, the findings of this study provide a hint that stimulation with steep SSH but not shallow SSH might engage nocifensive mechanisms as shallow SSH do not seem to influence the PAG in the same way as steep SSH.

Although our main focus in this study was the PAG, we found activations in two neighboring and functionally related areas, i.e., in NRD and RVM. The NRD is embedded in the ventromedial part of the PAG (Mantyh, 1982) and was shown to modulate responses caused by noxious stimulation of the spinal dorsal horn neurons by its descending projections (Yu et al., 1988). In addition, PAG and NRD project to the spinal cord indirectly via the RVM, which is situated centrally around the pontomedullary junction. It includes the NRM and the adjacent reticular formation. It is known to project diffusely to dorsal horn laminae, including superficial layers and deep dorsal horn structures (Fields and Heinricher, 1985). Similar to the PAG, the RVM has a dual role in pain control: it is as well able to inhibit and to facilitate nociceptive input and can thus be considered as the output of the midline pain-modulation system. Profound analgesia can be produced by stimulating the NRM which is due to a decrease in responsiveness of spinothalamic dorsal horn neurons to input from peripheral nociceptors (Besson and Chaouch, 1987). Alternatively, analgesia evoked by stimulation of the ventral sites of the PAG can be blocked by lesion of the RVM (Behbehani and Fields, 1979; Prieto et al., 1983). In the light of these data, activations found in the present study might mirror the descending pathway to the dorsal horn. These observations parallel the results of the present study that stronger activation in RVM can be observed in response to steep SSH.

We found stronger activation in response to steep SSH stimulation both in parts of the brain stem as well as in some other structures in the field of view, i.e., the PCC and the amygdala. As argued above, we suggest that stimulation with steep SSH might preferentially activate C-fiber input. In this sense, the fMRI results of our study are in line with previous studies that also found stronger activation to selective C-fiber stimulation compared to Aδ-fiber stimulation. Stronger activations have been reported in structures associated with the affective processing of nociceptive information (i.e., ACC (Qiu et al., 2006); anterior insula (Weiss et al., 2008)). Similar to the present study these authors (Qiu et al., 2006; Weiss et al., 2008) also did not find any stronger activation to selective Aδ-fiber stimulation when comparing it with selective C-fiber stimulation. This might be another hint to the correctness of our suggestion concerning preferential C-fiber activation by steep SSH stimulation.

Several limitations of our study have to be considered that might influence future research. First, the conditions steep and shallow SSH were determined by the different slopes of heating. Different slopes affect the frequency of the painful heat peaks that are essential for the paradigm. There are two possibilities to proceed further, with the same number of stimuli within a condition (i.e., 5× up and down) or the same duration within a condition, but a different number of stimuli within a condition. We decided to use the same number of stimuli to have the same number of painful events within a condition. However, this leads to different durations of stimulation between the two SSHs used. Future studies might explore the effects of the two types of SSHs using the same length but unequal number of painful events within a condition.

Second, the energy transmitted to the skin depends on the frequency and duration of stimulation within a condition. In our study, the transmitted energy (area under the curve) was higher in the shallow SSH condition. Future studies might utilize the same amount of transmitted energy. However, different slopes of heating will then request different durations of baseline between ramps. These segments in turn might rise additional percepts in difference to the heat stimulation that might influence the results. However, it should be mentioned that heat pain receptors start firing at about 43°C (Julius and Basbaum, 2001) so that it is quite difficult to produce ramps that have the same amount of energy in the painful range; moreover, it seems to be impossible to produce ramps with different SSH that have the same energy both in the noxious as well as in the innocuous temperature range. Taking this consideration into account, the difference in transferred energy above the temperature threshold of 43°C is smaller as compared to differences in transferred energy for the whole heating ramps.

Third (as mentioned earlier), the resolution of 2 mm × 2 mm × 2 mm might not be sufficient to detect further differentiation within the brain stem, especially within the PAG. Possibly, scanning with higher field strengths might identify a columnar organization of the human PAG.

In summary, we found stronger activation in the inferior part of the PAG and in the RVM in response to painful stimulation with steep SSH. These observations provide first evidence for selective activation of the midbrain structures PAG and RVM in the human brainstem by different SSH. Therefore, this stimulation can be used when human brainstem structures are in the focus of interest during nociception. The specific activation of the midbrain to steep SSH seems to be associated with the specific perception of second pain and might possibly be related to passive coping strategies.

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APPENDIX

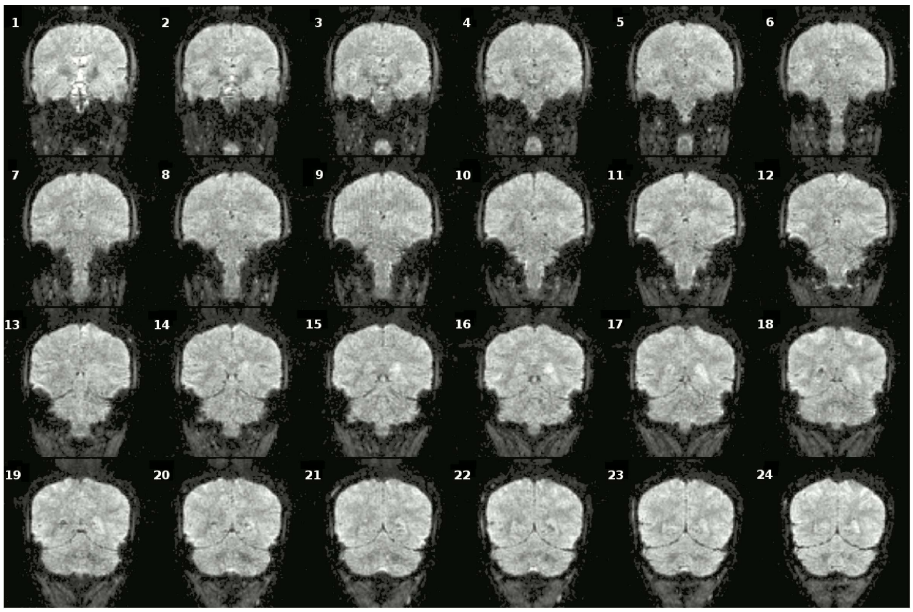

FIGURE A1 | Coronal slices (one volume) of fMRI data overlaid on a anatomical scan (neurological convention left = left).

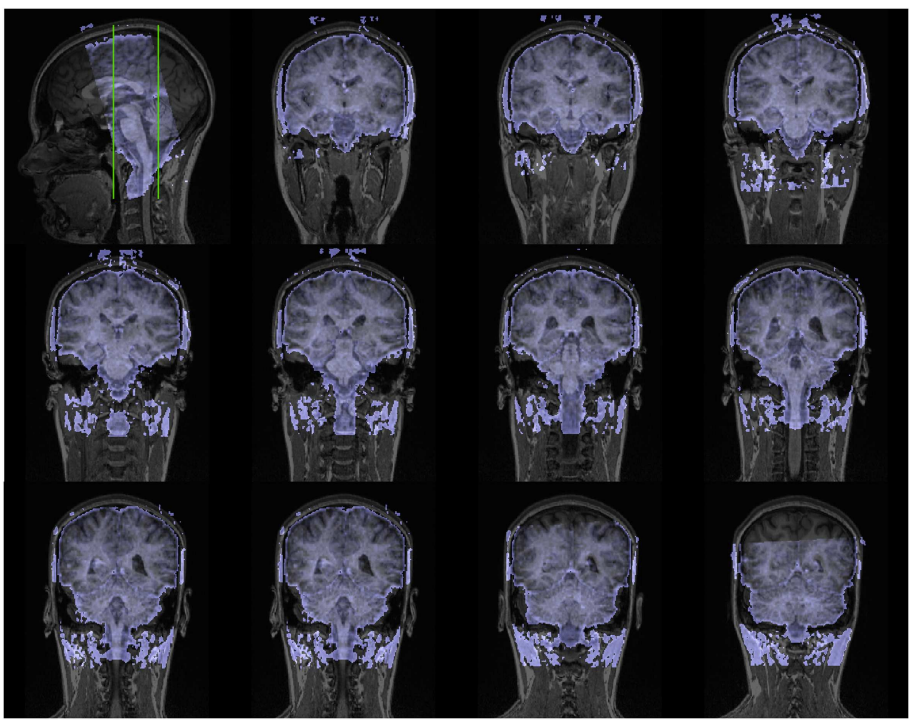

FIGURE A2 | Section (between green lines in mid – saggital view) of the functional mean BOLD – data coregistered to the anatomical scan (neurological convention left = left).

Manuskript III:

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Enhanced Brain Responses to Pain-related Words in Chronic Back Pain Patients and its Relation to Current Pain

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Abstract

Previous studies have found activations in parts of the so called “neuromatrix of pain” during the processing of pain-related words in healthy controls (HC) and pain-free migraine patients. The aim of the present study was to compare neural activations induced by pain-related words in a sample of chronic back pain (CBP) patients with activations in HC and to investigate the influence of current pain in CBP patients on this processing.
Eleven CBP patients and eleven HC matched for age and gender volunteered in the study. Subjects viewed pain-related, negative, positive, and neutral words and were asked to generate mental images during fMRI scanning. Activation was compared for contrasts between word categories and groups. We also investigated the relation to the current pain of patients.

In line with previous research, pain-related words (vs. baseline) activated a network of brain regions including anterior cingulate cortex (ACC) and right insula. There was higher activation in CPB patients vs. HC for pain-related vs. negative words in the subgenual ACC (sACC), prefrontal cortex, posterior midcingulate cortex, and bilateral anterior insula. Importantly, the amount of higher activation for pain-related vs. other words showed a positive linear relationship to current pain in some clusters (e.g. sACC, parahippocampal gyrus) in CBP patients.

These findings indicate not only an involvement of parts of the neuromatrix of pain in the processing of pain-related words which is stronger in patients, but also point to an overall enhanced processing of pain-related words in CBP patients.

Keywords: chronic back pain, semantic processing, current pain, fMRI

1. Introduction

Processing and perceptual evaluation of noxious events and its underlying neural substrate is strongly modulated by psychological variables such as attention [10; 32; 62; 63], emotional states [11; 22; 31; 36; 51; 58], expectations [8; 65], and learning [41; 68]. Thus, it was shown that environmental semantic and visual pain-related cues can induce neuronal activity in structures of the network which processes, among others, nociceptive information [29; 30; 35] within the human brain even when no noxious stimulus is applied [1; 39]. Based on the concept of Hebb's cell assemblies, it can be assumed that whenever we experience pain, its semantic and emotional representations become simultaneously activated and, therefore, associated with neural structures that process noxious events and constitute the experience of pain [7; 27]. Consequently, verbal material describing pain-related experience was found to alter pain itself [13; 47], and to activate neural structures engaged in the processing of noxious stimuli, e.g. anterior cingulate cortex (ACC), insula (INS), secondary somatosensory cortex (SII), prefrontal cortex (PFC), and parietal cortex [24; 46].

It has been shown that chronic back pain (CBP) patients differ from healthy controls (HC) in several characteristics of the brain, including structural [2], functional [3; 18], and neurochemical changes [56; 66]. Based on the described association between experience of pain, activation of structures involved in pain processing, and semantic representation of pain, it was suggested that chronic pain sufferers compared to healthy control subjects should develop a pain network with increased connectivity strength and efficacy due to repeated exposure to pain. Indeed, it was shown that chronic pain patients recall more pain-related autobiographical events in response to ambiguous words than healthy individuals, exhibit larger event-related potentials (ERPs) to painful stimuli [28; 38], and show altered ERPs when pain-related words are preceded by noxious stimuli [68]. In addition, activation of

the pain-processing structures was found when the pain-relevant aspects of the stimulus material were not in the focus of attention [14; 52; 57]. Furthermore, chronic pain patients showed enhanced electrophysiological activation in response to pain-related as compared to neutral words indicating that implicit pain memories may draw attention and enhance processing [19]. In summary, the perception of pain-related words leads to enhanced behavioral and neuronal responses even if semantic processing is precluded from conscious access. However, to the best of our knowledge there is no study investigating the relation between activation of pain-related words and current pain which also should influence the processing of pain-related words by continuously priming parts of the system processing the specificity of current pain.

So the present study was designed to test the following hypotheses based on previous results: *H1*. Pain-related words are able to induce processing in neural structures that, amongst others, can be activated by painful stimuli. *H2*. CBP patients compared to healthy controls show higher cortical activation during the processing of pain-related words in comparison to all other word categories and especially to negative words. *H3*. There is a linear relationship between current pain and the activation during the processing of pain-related words in CBP patients.

2. Methods

2.1. Patients and controls

Eleven patients with chronic back pain (10 women, 1 man; 23–56 years old, mean age = 43.7 years) and 11 healthy pain-free controls (10 women, 1 man; 24–58 years old, mean age = 45.2 years), matched for gender, age, and education, participated in this study as paid volunteers. Demographic and clinical characteristics of participants are summarized in Table 1.The CBP patients have been surveyed in medical interviews and met the following criteria: (1) minimum of 6 months history of low back pain; (2) pain had been classified as 'non-specific low back pain' (no indicators for nerve root problems, e.g. unilateral leg pain, radiating to foot or toes, numbness and/or paraesthesia; straight leg raising test induces leg pain); (3) magnetic resonance imaging (MRI) of the spine showed only age-related changes, but no spinal disorders or disc pathology; (4) no psychiatric disorders, no disease associated to small fibre pathology (e.g.; diabetes mellitus) according to clinical anamnesis, no other chronic disorder; (5) no use of medication for at least 48 hours before the experiment (requested before scanning). All participants were native German speakers and right-handed as assessed by the Edinburgh Handedness Inventory (EHI) [45]. All subjects were interviewed by a trained physician before the experiment to assess former pain episodes or current pain disorders. None of the healthy controls reported earlier lasting pain episodes (longer than one month), any neurological, psychiatric or other chronic disorder. Because depression may alter the processing of pain-related words [42], depressive symptoms were assessed with a German version of the Beck Depression Inventory-II (BDI-II) [26]. For the assessment of catastrophizing thoughts and persuasions, all subjects completed the Pain Catastrophizing Scale (PCS, [60]; German version: [40]). Participants in this study had been recruited by postings in the university or by verbal contact. In accordance with the Declaration of

Helsinki, written informed consent was obtained from each participant before the study, and the Ethics Committee of the Friedrich Schiller University approved the experiment.

Please insert table 1 here.

2.2. Verbal stimuli

Verbal stimuli included pain-related, non-pain-related negative, neutral, and positive adjectives. A total of 40 words were selected in a pilot study and rated for valence, arousal, and pain relevance. Pain-related adjectives, affectively negative adjectives, and positive adjectives were matched for arousal, and pain-related and affectively negative adjectives additionally were matched for valence. Furthermore, categories of words were also matched for the number of syllables and the frequency in German language (COSMAS II database, http://www.ids-mannheim.de/cosmas2/). For a more thorough description of stimuli selection and a detailed list of these stimuli, see Richter et al [52].

2.3. Experimental procedure

Examples of each word category were presented while participants were familiarized with the experimental procedure. Stimuli were projected via a video beamer onto a screen mounted on the head coil of the scanner. The experimental design is displayed in Fig. 1. Subjects were instructed to focus on the semantics of the words by generating a mental image of a situation associated with the word. To increase compliance, subjects were told that after the experiment they would be asked to give examples of their imaginations. Word stimuli were presented in 16 blocks (4 blocks of each word category). The blocks consisted of 5 words (belonging to one word category); each word was displayed for 4.1 seconds, followed by a blank screen for 0.1 second. Each block was followed by a delay phase in which a fixation cross was presented for 11 seconds and a subsequent decision interval of 7

seconds duration. During the decision interval, subjects were requested to choose the correct word category from 2 categories presented (e.g., A = pain-related; B = negative). Subjects responded via a magnetic resonance imaging (MRI)–compatible button response box fixed under their right hand. After the decision, a fixation cross was presented as a baseline condition for 13 seconds. Each word was presented 2 times throughout the experiment. The order of the words within the block and the order of the blocks were pseudo-randomized with the restriction that the same word category was not presented twice in succession. The whole fMRI run took 14 minutes.

After the scanning session, participants rated the mean valence, arousal, and pain relevance of each word category on a 10-point numerical rating scale (NRS), with low scores indicating low arousal and negative valence, and high scores indicating high arousal and positive valence. Following the scanning procedure, all subjects rated their current back pain on a VAS (0 = “no pain”, 10 = “worst pain imaginable”). The pain ratings were obtained at the end of the experiment because we wanted to avoid any distraction from our cognitively demanding paradigm, such as rating pain during the time between the imagination task and the rating of the valence of the verbal material. Furthermore, a rating of task difficulty was quoted on a VAS (0 = “very easy”, 10 = “very difficult”)

Please insert figure 1 here.

2.4. Analysis of behavioral data.

All statistical calculations were carried out using IBM SPSS Statistics 19 (IBM, Armonk, NY, USA). Normal distribution of behavioral data was determined by Kolmogorov-Smirnov Test and Levene’s test was applied to assess the equality of variances across the two groups. Variables that followed a normal distribution were statistically analyzed using Student’s t-

test. Variables that were not distributed normally were analyzed with χ^2-tests. Welch's t-test was utilized for variables with unequal variances across groups. We tested for differences between CBP patients and HC concerning the rating dimensions (arousal, valence, and pain relevance) of word material. Therefore, separate two-way, repeated measures ANOVAs for mixed experimental design (between-subject factor Group and within-subject factor Word Category) were conducted. We considered values of $P < 0.05$ to be statistically significant.

2.5. fMRI-data acquisition and analysis

In a 3-Tesla magnetic resonance scanner (Tim Trio, Siemens, Medical Systems, Erlangen, Germany), 305 volumes were measured using a T2* weighted echo-planar sequence (time to echo [TE] = 30 ms, flip angle = 90°, matrix = 64 x 64, field of view [FOV] = 192 mm, scan repeat time [TR] = 2.8 s). Each volume comprised 40 axial slices (thickness = 3 mm, no gap, in-plane resolution = 3 x 3 mm) parallel to the intercommissural plane (AC–PC-plane). Additionally, a high-resolution T1- weighted anatomical volume was recorded (192 slices, TE = 5 ms, matrix = 256 x 256 mm, resolution = 1 x 1 x 1 mm). Imaging data were pre-processed and analyzed using BrainVoyagerQX, Version 2.3 (Brain Innovation, Maastricht, The Netherlands) and NeuroElf. V0.9 c. (http://.neuroelf.net).

The volumes were realigned to the first volume in order to minimize the effects of head movements on data analysis. Further data pre-processing comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) as well as temporal smoothing (high pass filter: 3 cycles per run). Anatomical and functional images were co-registered and normalized to the Talairach space [61]. Statistical analysis of fMRI-data was performed by multiple linear regression of the signal time course at each voxel. The expected blood oxygen level-dependent (BOLD) signal change for each event type (predictor) was modeled by a

canonical hemodynamic response function (modified gamma function). Voxel-wise analyses were inspected within the whole brain. To strike a balance between type I and type II errors, we tested whether the detected clusters survived a correction for multiple comparisons. We used the approach as implemented in Brain Voyager which is based on a 3D extension of the randomization procedure described by Forman et al. (1995) [21; 23]. First, voxel-level threshold was set at $p < 0.01$ (uncorrected). Threshold maps were then submitted to a correction for multiple comparisons for each contrast. The correction criterion was based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold yielding a cluster level false-positive rate of 5% was applied to the statistical maps of each contrast [59]. All clusters reported in this article survived this ROI-based control of multiple comparisons. Every reported contrast was derived from general linear models (GLMs) utilizing the random-effects approach. Main effects were analyzed for the contrast between pain-related words vs. baseline (hypothesis 1; H1). Main effects and separate interaction analyses including the factor Group were performed for the relevant contrasts between the word categories according to H2: pain-related vs. all other word categories (neutral, positive, negative) and pain-related vs. negative words.

In the next step, we analyzed correlations between VAS pain ratings after the scanning procedure with the relevant differences of parameter estimates (difference: pain vs. negative, pain vs. (negative, neutral, positive)) for the group of the CBP patients only (control subjects were excluded because they had no pain, so there is no variance in these parameters allowing a correlative analysis) (H3).

3. Results

3.1. Questionnaire and behavioral data

Questionnaire data. On average, CBP patients reported significantly higher current pain ratings (M = 2.68, SD = 1.23) than healthy controls (HC) (M = 0.91, SD = 0.16), *Welch's* $t(10.181) = 4.02$, $p = .002$ (Table 1). Also, total BDI-2 scores of CBP patients (M = 8.36, SD = 5.39) were significantly higher compared to HC (M = 2.36, SD = 1.80), *Welch's* $t(12.213) = 3.501$, $p = .004$ (Table 1). According to BDI-scores, only one patient showed signs of a clinically meaningful depression (score of 20; [26]). Main results remain essentially unchanged when excluding this subject from analyses, so we decided not to exclude this subject. There was no significant difference between groups in pain catastrophizing according to the Pain Catastrophizing Scale (PCS), neither for the total score nor for subscale scores (Table 1).

Behavioral data. During the experiment, all participants categorized the words properly ($M_{CBP} = 15.36$ and $M_{HC} = 15.09$ correct out of 16 judgments, see Table 1).

To verify whether CBP patients and HC differ in their ratings (regarding post-scanning arousal, valence, and pain relevance) of the word categories, we conducted three separate two-way, repeated measures ANOVAs. Mean ratings of valence, arousal, and pain relevance for the different word categories are depicted in Fig. 2. *Valence:* As expected, words of different categories were rated differently on the valence dimension as indicated by the significant main effect of Word Category ($F(3, 54) = 910.82$, $p < .001$). No significant main effect of Group on valence ratings was observed ($F(1, 18) = 1.45$, $p = .244$). However, the interaction of Word Category*Group was significant ($F(3, 18) = 10.35$, $p < .001$), suggesting

that the effect of the factor Word Category on valence ratings was modulated by Group. Contrasts for the interaction term were performed by comparing the pain-related word category to the remaining categories to follow up the interaction effects: The analysis revealed significant contrasts for neutral vs. pain-related words ($F(1,18) = 7.11$, $p = .016$) and positive vs. pain-related words ($F(1,18) = 12.50$, $p = .002$). Importantly, no significant interaction Word Category*Group was observed for the contrast negative vs. pain-related words ($F(1,18) = 0.214$, $p = .65$). *Arousal:* Mauchly's test indicated that the assumption of sphericity was violated for the main effect of Word Category, ($\chi^2(5) = 11.79$, $p = .038$). Therefore, degrees of freedom were corrected using Greenhouse–Geisser estimate of sphericity ($\varepsilon = 0.67$). As expected, there was a significant main effect of the factor Word Category on arousal ratings ($F(2.03, 36.44) = 162.79$, $p < .001$), with pain-related words rated as more arousing than neutral words ($F(1, 18) = 505.21$, $p < .001$). No significant contrast was observed for the comparison between pain-related and positive words as well as between pain-related and negative words. There was also a significant main effect of Group on arousal ratings ($F(1, 18) = 2862.18$, $p < .001$) with CBP patients showing lower arousal ratings than HC. This result goes in line with the valence data for the group showing a tendency towards more neutral ratings for salient (positive, negative, pain-related) words in CBP patients. No significant interaction Word Category*Group was observed ($F(2.03, 36.44) = 1.09$, $p = .349$). *Pain Relevance:* A repeated measures ANOVA confirmed the effect of Word Category on the rating scores of pain relevance ($F(1.90, 34.34) = 558.04$, $p < .001$). Contrasts of the factor Word Category confirmed that pain-related words were rated as more pain relevant than negative ($F(1,18)=484.13$, $p < .001$), neutral ($F(1,18)=910.41$, $p < .001$), and positive words ($F(1,18)=923.06$, $p < .001$). There was no significant main effect of Group

(*F*(1,18) = 0.196, p = .663) and no significant interaction Word Category*Group (*F*(1.90, 34.34) = 2.334, p < .114).

Please insert figure 2 here.

3.2. Imaging

H1: Neural activation of pain-related words

Both chronic back pain (CBP) patients and healthy controls (HC) showed a similar network of activated brain regions in response to pain-related words vs. baseline. This network includes among others the striate and extrastriate cortex of the occipital lobe extending into the left fusiform gyrus, widely distributed activations in the frontal lobe bilaterally, bilateral supplementary motor area (SMA), pre-SMA, the anterior cingulate cortex (ACC), and the insula (INS) (Supplementary Table 1). These activations were expected as based on the nature of the paradigm [14; 52]. They are in line with our first hypothesis (H1).

The comparison between activations during the processing of pain-related vs. all other word categories (negative, neutral, and positive words) independently of factor Group (main effect) reveals activations in the right anterior INS, the right DLPFC, in the right parietal cortex, and in the dorsomedial prefrontal cortex (DMPFC) (Supplementary Table 2).

Comparing activations during the processing of pain-related vs. negative words shows clusters of activation in several regions, including the parietal cortex (inferior parietal lobule, supramarginal gyrus), subgenual ACC (sACC), posterior midcingulate cortex (pMCC), brainstem (pons), right fusiform gyrus, bilaterally medial temporal gyrus, cuneus, right hemisphere dorsolateral prefrontal cortex (DLPFC), and cerebellar structures (Supplementary Table 3).

H2: Effects of group and word category

The contrast for the interaction Group*Word category (pain-related vs. all other word categories) revealed increased activations in CBP patients bilaterally in the anterior INS, the OFC, the fusiform gyrus, and in the cerebellum (Supplementary Table 4). Importantly, the interaction contrast between Group and Word category (pain-related vs. negative words) revealed increased activations in CBP patients in several regions, including the INS (bilaterally), posterior midcingulate cortex (pMCC), VLPFC bilaterally, the orbitofrontal cortex (OFC) (Fig. 3A and Table 2). These results are in line with hypothesis 2.

Please insert figure 3 here.

H3: Correlation analyses of word category in CBP patients

A correlation analysis between current pain ratings (VAS) and the differences in activation between pain-related (weighted 3 times according to the other word categories) vs. all other word categories (negative, neutral, and positive words) revealed clusters of positive correlation in the parahippocampal gyrus bilaterally, the left sACC, and head of the caudate (Fig. 3B and Table 3). For the correlation analysis between current pain ratings (VAS) with the differences in activation between pain-related vs. negative words, we found clusters of negatively correlated activity in orbitofrontal cortex, in the right insula, posterior cingulate cortex, the fusiform gyrus as well as in the basal ganglia and cerebellar structures (Fig. 3C and Table 3).

Please insert table 2-3 here.

4. Discussion

The present fMRI study revealed several important results. First, we confirmed previous findings (Richter et al., 2010; Eck et al., 2011) that showed an increase of activation during the processing of explicitly attended pain-related words in several regions of the brain including parts of the neuromatrix of pain. So we found activated brain areas that are associated with the processing of affective and attentional aspects of pain when comparing pain-related words with words from all other categories and specifically with negative words. Second, patients suffering from chronic back pain (CBP) showed higher activations than matched control subjects for pain-related in comparison to all other word categories or specifically with negative words in several structures including the insula and parts of the cingulate cortex. Third, we found linear relationships between current pain and activations in CBP patients in a variety of neural structures which are relevant for the processing of pain.

4.1. H1: Neural activation of pain-related words vs. baseline

Pain-related words activate brain regions associated with the neuromatrix of pain, i.e. the postcentral gyrus (SI), the anterior INS, the precentral gyrus (MI), pre-supplementary motor area, and DLPFC which correspond to activations found during similar language tasks [14; 52]. This indicates that the processing of pain-related words seems able to activate structures consistently found activated during the processing of nociceptive information [1; 48; 54]. Exemplarily, the anterior INS is thought to be engaged in the processing of emotional aspects of pain and pain imagination [1; 44; 50; 67].

We also found activations in (extra)striate cortex extending to medial temporal gyrus and including the fusiform gyrus, and in the parietal cortex. These structures have been

shown to be activated during visual processing including activation during reading and/or directed attention towards visually presented verbal materials [25; 55].

In line with previous findings [52], the comparison of pain-related and negative words revealed enhanced activation in several brain regions including sACC, pMCC, PPC, and pons. The sACC might be associated with its function in attentional focusing towards the more threatening and salient (here pain-relevant) stimuli [52]. The activation in the pMCC is concerned with the orienting of the body in response to sensory, including noxious stimuli [64]. Thus, pain-related words are likely more relevant than negative words for the revision of the orientation of the body. This explanation would also account for the activation of the PPC. Moreover, we found the pons activated. Most of the midbrain circuitry is involved in pain modulation, with extensive connections to the reticular system of the brainstem. Thus, pain-related words might possibly influence the descending pathways influencing on the processing of incoming nociceptive information. In support of this notion, placebo effects induced by verbal manipulation have been shown to influence both pontine structures and spinal cord [15; 16].

4.2. H2: Effects of group and word category

When investigating interaction effects, CBP patients showed higher activations than HC in the contrast pain-related vs. negative words bilaterally in the anterior INS, pMCC, and right hemisphere of OFC. Except for the pMCC, these clusters are also activated in the comparison between pain related vs. negative, neutral, and positive words. The anterior INS has been shown to integrate information about salience of a given stimulus [35; 69], indicating its ability to capture attention [29]. Thus, activation of the anterior INS is probably not merely associated with the painfulness of a stimulus but also with its saliency for the

bodily integrity [9]. Therefore, the higher activation in CBP patients points to an enhanced awareness for threatening, potentially painful cues in the environment and a generally heightened salience of pain-related materials for subjects characterized by frequent pain events. The concomitant activation of the pMCC might be interpreted as a greater threat-related bias in CBP patients towards pain-related stimulus material: Together with body orientation to the threatening event (see 4.1), saliency has been shown to be processed in the midcingulate cortex [69]. As suggested by these results, pain–related words are of higher significance as compared to negative words as well as to words of all other categories (negative, neutral, and positive) for CBP patients. This emphasis might be due to learning processes against the background of chronic pain: The experience of persistent pain leads to a higher sensibility for nociceptive information [17] as well as for pain- associated information [18; 20], e.g. pain-related words [19]. Thus, it seems possible that CBP alters the pain- processing neuronal network in a way that associations to pain-related verbal cues get more excitable.

The OFC has been proposed to be involved in representing the affective value of reinforcers, in sensory integration, and in expectation [5]. In particular, the human OFC is thought to regulate planning behavior associated with the reward value of primary reinforcing stimuli such as taste, touch, and pain [33; 34; 37; 70]. Therefore, we hypothesize that the OFC is activated by visual pain-related information when both pain as primary negative reinforcer as well as visual pain-relevant stimuli as our descriptors were previously processed simultaneously. Roy et al [53] has also shown that the OFC is stronger activated by negative than by positive emotional pictures. Thus, we suggest that the activation in the CBP patients group is stronger due to their enhanced affective involvement while viewing pain-related as compared with negative words. This result is also in line with Eck and colleagues

[14], who found a stronger activation in the OFC when comparing migraine sufferers with HC when they viewed pain- related vs. negative words.

4.3. H3: Relationship to current pain

The correlation analysis between current pain rating (VAS) and differences in activation between pain-related and all other categories of words revealed positive correlations, e.g. for the sACC and the parahippocampal complex. SACC has been shown to be involved in the processing of emotional aspects of pain (see above), but also in the processing of anxiety and stress [48]. This result suggests that higher current pain elevates the emotional salience and stress relevance of pain-related words. Possibly, attention is preferably focused on potential painful threats in the environment. Therefore, we have to suggest that chronic pain patients are more sensitive for pain-related information under conditions of current pain.

We also found a positive correlation between current pain and the activation bilaterally in the parahippocampal formation. Activation in this area has been associated with painful stimulation [12], with the detection of potential painful aspects in the environment [6; 53], or has been found in paradigms where pain was modulated by expectation or anxiety [49]. Thus, this correlation points to a generally enhanced susceptibility for pain-related verbal cues of subjects suffering from CBP.

The correlation analysis between current pain rating (VAS) and differences in activation between pain-related vs. negative words revealed negative correlations, e.g. for the OFC and aINS. The higher current pain is CBP patients suffer from, the lower the activation is in these structures. This result is in line with previous reports. Thus, Derbyshire et al [12] found a negative correlation between experimental pain ratings and the activation

in the OFC. Likewise, Bantick and colleagues [4] reported higher OFC activation when subjects gave lower pain ratings. The OFC is associated with the processing of reward value [43]. The negative correlation might point to reduced activation in OFC the higher the negative value of pain-related words is. An alternative interpretation for the negative correlations might be that higher current pain results in a constantly high activation of these structures that does not allow additional activation by pain-related words. This additional activation might then depend on the pre-activation by current pain.

4.4. Study limitations

A limitation is the relative low number of participants. However, strict inclusion criteria and exact matching in gender and age allowed to find significant results even with 11 subjects per group. Future research may attend to the questions of whether the obtained results can be generalized to other pain conditions and to situations in which the verbal material is not attended explicitly.

4.5. Conclusion

In summary, the present results revealed that CBP patients were characterized by enhanced responses within the pain processing network compared with healthy subjects. Importantly, current pain was positively related to activation to pain-related words in brain areas associated with affective pain processing. This result is in accordance with the associative network theory.

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Figure legends:

Figure 1:

Stimulus protocol.

Figure 2:

Mean ratings (SD) of valence, arousal, and pain relevance of each word category for CBP patients and HC. Valence (0 = “negative”; 10 = “positive”), arousal (0 = “no arousal”; 10 = ”maximal arousal”), and pain relevance (0 = “not relevant”; 10 = “highly relevant”) .

Figure 3:

(A) Activation maps illustrating the interaction between group (CBP patients vs healthy controls) and word category (pain-related vs. negative adjectives); left: z = 1, right: x = 3 **(B)** Correlation of current pain (VAS, post scanning) with the contrast pain-related vs. negative, neutral, and positive adjectives in CBP patients; z = -10 **(C)** Correlation of current pain (VAS, post scanning) with the contrast pain vs. negative adjectives in CBP patients; x = 44.

Activations are superimposed on a Talairach template (average of all subjects), displayed in neurological convention.

Figure 1

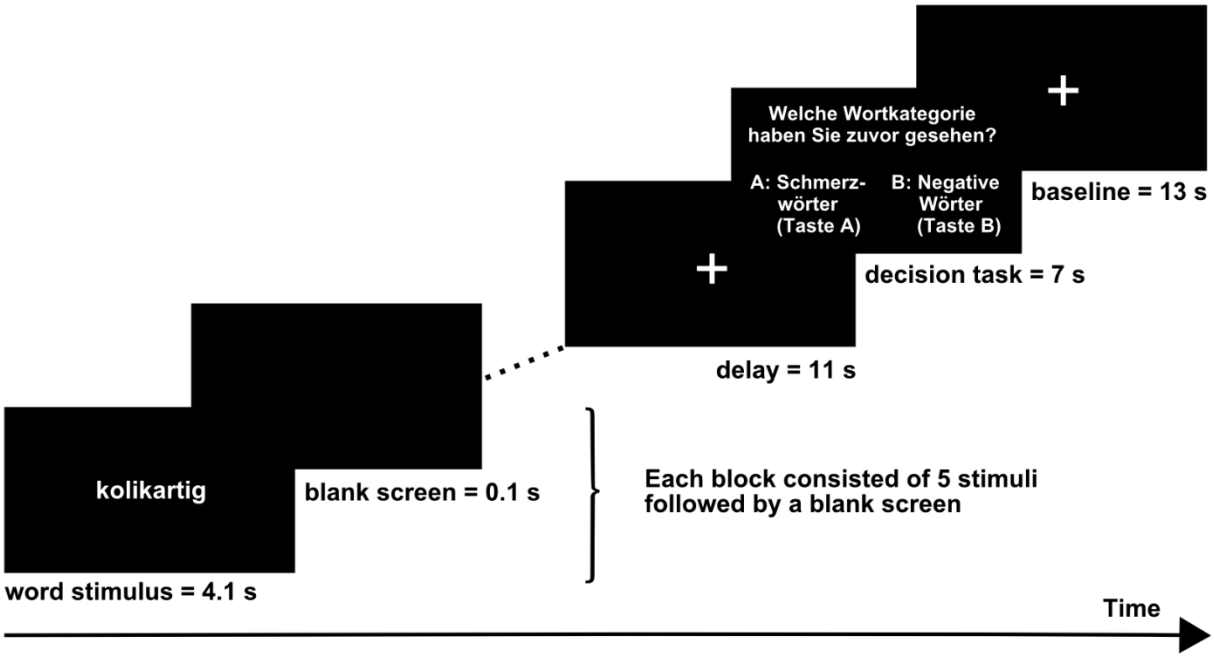


Figure 2

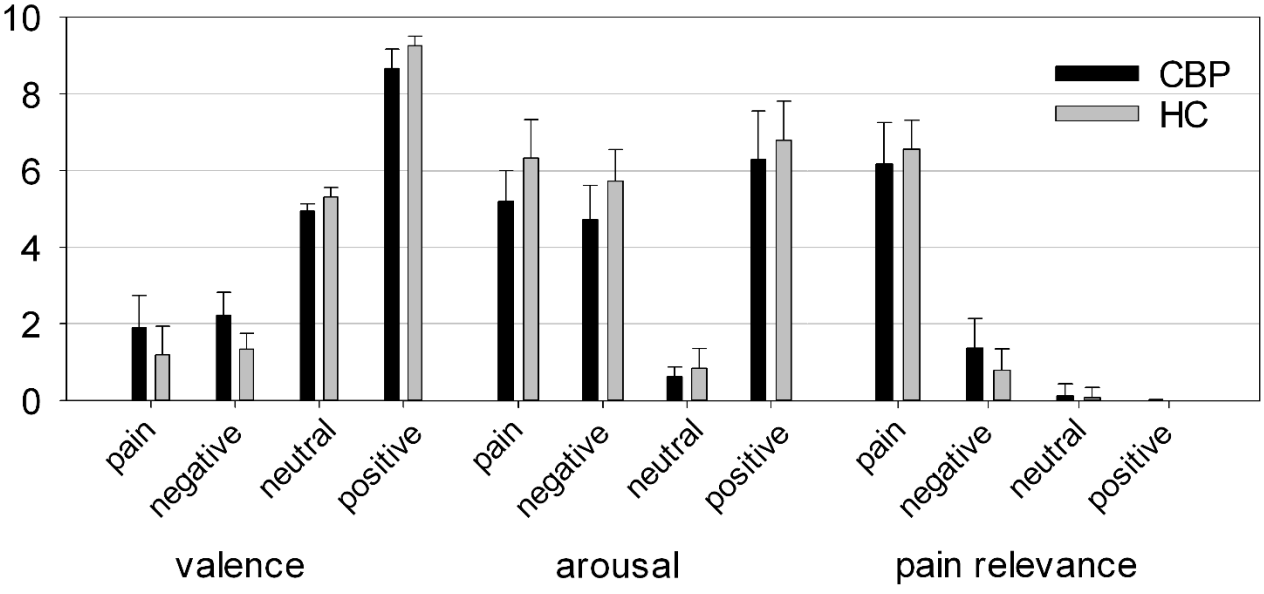
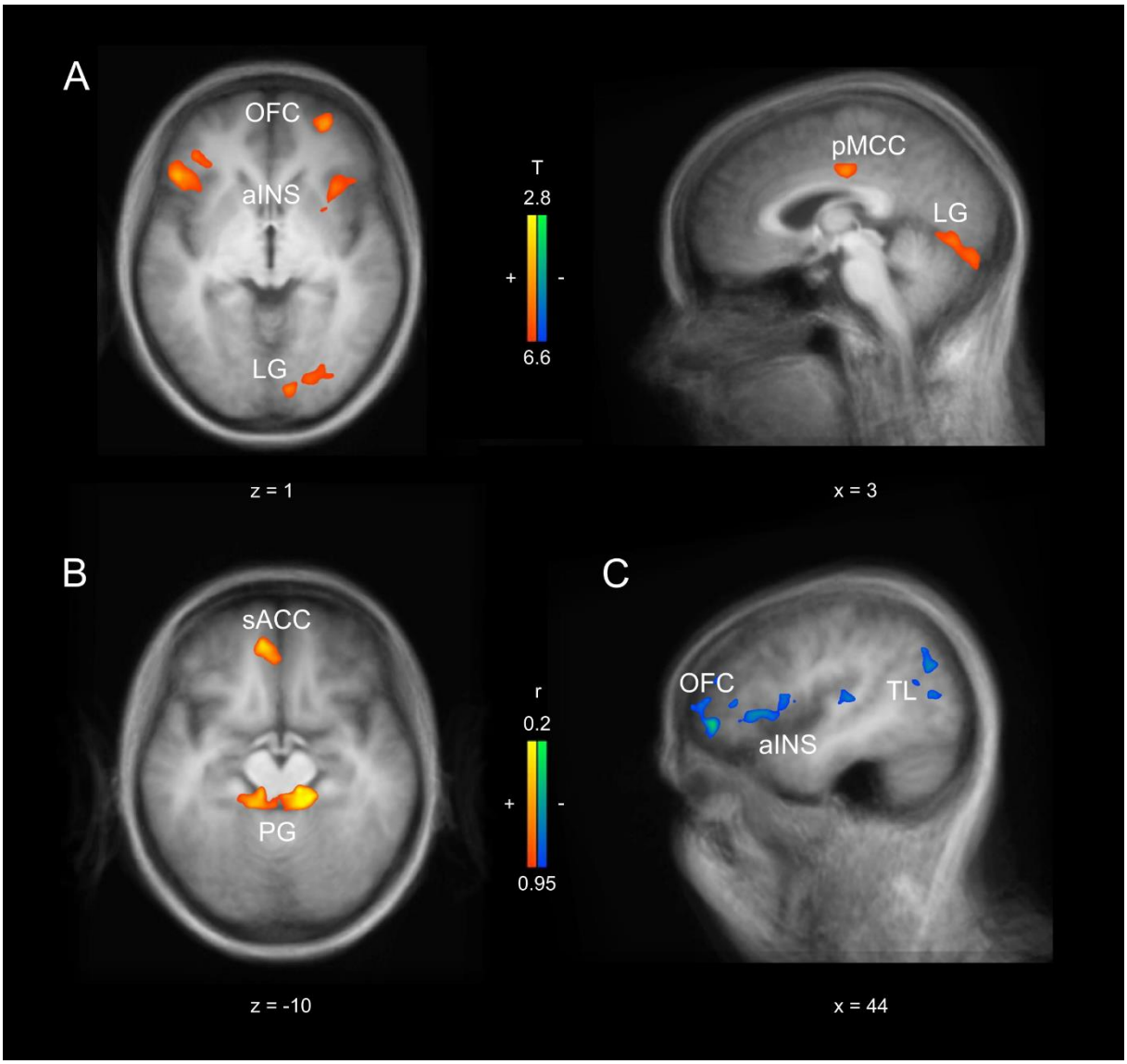


Figure 3


A
OFC
aINS
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z = 1
T
2.8
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6.6
pMCC
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x = 3
B
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PG
z = -10
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0.2
+
-
0.95
C
OFC
aINS
TL
x = 44

Table 1. Demographic and clinical characteristics as well as behavioral data of chronic back pain patients (CBP) and healthy controls (HC)

	CBP	**HC**			
Sex					
Male / Female	1 / 10	1 / 10			
Age (in years):	43.73 ±13.15	45.18 ±10.56			
Range	23-56	24-58			
Pain history					
6 –12 months	N = 2	N = 0			
2 – 5 years	N = 3	N = 0			
> 5 years	N = 6	N = 0			
Pain intensity			***t***	***df***	***p***
Mean pain intensity (VAS[a] recent 4 weeks)	3.32 ±0.56	0.09±0.30	5.719	10.53	<.001
Strongest pain (VAS recent 4 weeks)	5.14 ±1.85	0.27±0.90	6.268	12.76	<.001
Spontaneous pain (VAS post scanning)	1.72 ±1.34	0.05±0.15	4.152	10.25	.002
BDI[b] score	8.36 ±5.39	2.36 ±1.80	3.501	12.12	.004
Pain Catastrophizing Scale (PCS)	15.91 ±4.20	11.82 ±7.04	1.654	20	.114
Rumination	6.18 ±3.18	5.09 ±3.27	0.792	20	.437
Helplessness	5.36 ±2.97	4.00 ±2.61	1.143	20	.267
Magnification	4.36 ±1.96	2.73 ±2.19	1.843	20	.080
Task difficulty[c]	1.55 ±1.57	1.00 ±1.09	0.944	20	.356
			χ²		
Correct word categorization[d]	15,36 ±0.81	15,09 ±1.58	0.034	1	.853

Note: Values are mean ± SD; [a]Visual Analogue Scale (VAS): 0 = ‘‘no pain’’, 10 = ‘‘strongest pain imaginable"; [b]BDI = Beck Depression Inventory; [c]Visual Analogue Scale (VAS): 0 = “very easy”, 10 = “very difficult”; [d]correct categorizations out of 16 judgments

Table 2. Activations to pain-related versus negative words in the comparison between CBP patients and HC

x	y	z	Cluster size	t-value	Brain region		Brodmann area
26	-76	-32	72	5,210	Pyramis	R	/
-51	22	4	30	4,921	Inferior Frontal Gyrus	L	47
-44	12	-7	20	4,600	Superior Temporal Gyrus	L	38
45	18	12	14	4,492	Inferior Frontal Gyrus	R	44
68	-61	25	8	4,336	Superior Temporal Gyrus	R	39
-20	-96	-20	37	4,281	Fusiform Gyrus	L	18
19	-26	37	11	4,254	Cingulate Gyrus	R	31
0	-76	57	10	4,235	Precuneus	L	7
0	58	40	21	4,126	Medial Frontal Gyrus	L	9
38	15	2	8	4,023	Insula	R	/
35	50	2	13	3,939	Middle Frontal Gyrus	R	10
27	-83	17	11	3,914	Middle Occipital Gyrus	R	19
-63	9	19	7	3,889	Inferior Frontal Gyrus Insula	L	45
-13	-97	17	17	3,782	Middle Occipital Gyrus	L	18
31	-70	7	19	3,695	Posterior Cingulate	R	30
3	-15	31	10	3,635	Cingulate Gyrus	R	23
8	-85	4	19	3,474	Lingual Gyrus	R	17
-13	-73	-3	8	3,343	Lingual Gyrus	L	18
-47	51	33	7	3,304	Middle Frontal Gyrus	L	9
-44	34	2	8	3,244	Inferior Frontal Gyrus	L	45
53	-56	29	7	3,135	Superior Temporal Gyrus	R	39
-34	-44	7	22	-4,912	Caudate (Caudate Tail)	L	/
-23	42	37	8	-4,348	Superior Frontal Gyrus	L	9
-27	9	38	37	-4,315	Middle Frontal Gyrus	L	8
28	-10	4	7	-4,220	Lentiform Nucleus (Putamen)	R	/
67	3	-3	8	-4,192	Superior Temporal Gyrus	R	22
7	5	-5	20	-4,124	Caudate (Caudate Head)	R	/
53	41	14	9	-4,081	Middle Frontal Gyrus	R	46
55	32	10	13	-4,066	Inferior Frontal Gyrus	R	46
28	-13	27	15	-4,026	Insula	R	13
-55	-52	6	12	-3,979	Middle Temporal Gyrus	L	39
-6	-12	-10	7	-3,931	MidbrainSubstania Nigra	L	/
25	-42	47	11	-3,872	Paracentral Lobule	R	5
69	7	15	7	-3,779	Precentral Gyrus	R	6
-11	-17	-24	8	-3,575	Parahippocampal Gyrus	L	28
-22	18	63	7	-3,454	Superior Frontal Gyrus	L	6
-29	20	-22	12	-3,297	Inferior Frontal Gyrus	L	47

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuroanatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described.

Table 3. Mean centers of mass of clusters that are significantly correlated with current pain during the experimental fMRI run in CBP patients.

x	y	z	Cluster size	r	Brain region		Brodmann area
Pain-related words vs *all other word categories*:							
14	-30	-4	35	0,919	Parahippocampal Gyrus	R	30
-14	-32	-6	24	0,888	Parahippocampal Gyrus	L	30
-2	36	-6	23	0,882	Anterior Cingulate	L	32
3	7	17	27	-0,811	Caudate	R	/
Pain-related vs *negative words:*							
9	-43	-7	72	-0.950	Culmen	R	/
6	-85	-13	86	-0.926	Lingual Gyrus	R	18
16	-2	22	39	-0.916	Caudate (Caudate Body)	R	/
-36	-15	38	60	-0.914	Precentral Gyrus	L	4
-41	-32	40	L	-0.857	Inferior Parietal Lobule	L	40
47	39	1	31	-0.910	Inferior Frontal Gyrus	R	46
3	-73	18	41	-0.895	Cuneus	R	18
-10	-72	-5	96	-0.893	Lingual Gyrus	L	18
-22	-60	-9	L	-0.847	Fusiform Gyrus	L	19
-6	-4	17	38	-0.886	Caudate (Caudate Body)	L	/
-6	-18	8	L	-0.869	Thalamus (Medial Dorsal Nucleus)	L	/
3	-58	5	50	-0.885	Posterior Cingulate	R	30
50	12	5	59	-0.881	Insula	R	/

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuro-anatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Activations to pain-related words versus baseline

x	y	z	Cluster size	t-value	Brain region		Brodmann area
-43	-64	-3	1463	10,59	Inferior Temporal Gyrus, Middle Occipital Gyrus, Inferior Occipital Gyrus, Parahippocampal Gyrus, Superior Temporal Gyrus	L	37, 18, 19, 22
30	-88	4	1489	10,04	Middle Occipital Gyrus, Inferior Occipital Gyrus	R	18, 19
-55	30	13	1661	9,572	Inferior Frontal Gyrus, Middle Frontal, Precentral Gyrus, Superior Temporal Gyrus, Anterior Insula, Postcentral Gyrus	L	46, 9, 7, 22, 46, 43, 10
-8	16	50	291	8,397	Superior Frontal Gyrus, Medial Frontal Gyrus, Middle Frontal Gyrus	R/L	8,47
-28	-50	37	172	5,710	Superior Parietal Lobule	L	7
48	-10	25	137	5,158	Precentral Gyrus, Postcentral Gyrus, Inferior Frontal Gyrus	R	6, 3, 44, 9
43	28	8	55	4,199	Inferior Frontal Gyrus	R	13
16	-62	23	4354	-8,486	Precuneus, Cuneus, Middle Temporal Gyrus, Lingual Gyrus, Parahippocampal Gyrus, Superior Occipital Gyrus, Superior Temporal Gyrus, Posterior Cingulate, Sub-Gyral (Hippocampus), Cingulate Gyrus, Inferior Parietal Lobule, Paracentral Lobule	R/L	31, 18, 7, 19, 31, 39, 29, 24, 40, 5
8	51	8	878	-7,695	Medial Frontal Gyrus, Anterior Cingulate	R/L	10, 32, 24, 9
23	42	34	99	-4,628	Superior Frontal Gyrus, Middle Frontal Gyrus	R	9, 8
55	-36	38	137	-4,601	Inferior Parietal Lobule, Supramarginal Gyrus, Postcentral Gyrus	R	40, 49
54	-8	-10	130	-4,524	Superior Temporal Gyrus, Middle Temporal Gyrus	R	22, 21

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuroanatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described

Supplementary Table 2: Activations to pain-related words versus negative, neutral, and positive words

x	y	z	Cluster size	t- value	Brain region		Brodmann area
40	25	2	142	6.255.350	Insula, Inferior Frontal Gyrus , Precentral Gyrus , Superior Temporal Gyrus	R	47, 45, 44, 22
21	36	-4	26	5.516.290	Middle Frontal Gyrus	R	11, 44
42	-38	36	45	4.839.195	Supramarginal Gyrus	R	/
12	-52	-15	63	4.595.317	Culmen, Declive, Uvula	R	/
48	48	6	104	4.495.284	Inferior Frontal Gyrus , Middle Frontal Gyrus	R	46, 10
-61	-58	28	16	3.948.799	Superior Temporal Gyrus	L	39
0	15	-3	11	3.780.246	Anterior Cingulate	L	25
-63	-47	10	11	3.762.343	Middle Temporal Gyrus	L	21
-4	31	42	14	3.675.093	Medial Frontal Gyrus	L	8
-54	21	14	16	3.579.018	Inferior Frontal Gyrus	L	45
-36	-75	35	11	-4.994.986	Precuneus	L	19
-60	-85	-16	11	-4.529.283	Tuber	L	/
0	20	-17	20	-4.335.946	Medial Frontal Gyrus	L	25
-22	0	-4	21	-4.223.686	Lentiform Nucleus (Putamen)	L	/
45	-19	-8	16	-3.309.815	Superior Temporal Gyrus	L	22

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuroanatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described.

Supplementary Table 3: Activations to pain-related versus negative words

x	y	z	Cluster size	t- value	Brain region		Brodmann area
50	-60	-30	46	5,501	Tuber	R	/
0	-39	-30	73	5,465	rostral pons	R	/
0	12	-2	23	4,769	Anterior Cingulate	L	25
48	48	6	9	4,577	Inferior Frontal Gyrus	R	46
42	-38	34	33	4,504	Supramarginal Gyrus	R	40
15	-56	-16	33	4,481	Culmen	R	/
-19	-88	39	9	4,222	Cuneus	L	19
0	-20	23	11	4,179	Cingulate Gyrus	L	23
-43	-48	51	59	4,156	Inferior Parietal Lobule	L	40
-40	-50	14	15	4,023	Middle Temporal Gyrus	L	39
36	-44	65	12	3,872	Postcentral Gyrus	R	5
-20	-79	14	13	3,862	Cuneus	L	17
45	41	-10	9	3,732	Middle Frontal Gyrus	R	11
-17	-19	-23	10	3,709	Parahippocampal Gyrus	L	28
47	-40	-7	18	3,666	Fusiform Gyrus	R	37
-28	-28	72	8	3,617	Postcentral Gyrus	L	3
66	-6	21	10	3,482	Precentral Gyrus	R	4
61	37	-3	10	3,384	Inferior Frontal Gyrus	R	47
55	-41	1	9	3,049	Middle Temporal Gyrus	R	22
27	-59	50	97	-6,574	Superior Parietal Lobule	R	7
-3	-45	57		-3,754	Precuneus	L	7
13	-58	55		-3,590	Precuneus	R	7
-3	-36	64		-3,405	Paracentral Lobule	L	4
-55	-17	38	12	-6,264	Postcentral Gyrus	L	4
48	-18	48	173	-6,022	Postcentral Gyrus	R	3
57	-14	35		-4,137	Precentral Gyrus	R	4
52	-2	38		-3,105	Precentral Gyrus	R	6
36	-78	29	43	-5,610	Superior Occipital Gyrus	R	19
-33	-75	33	46	-5,556	Superior Occipital Gyrus	L	39
-27	7	50	19	-5,017	Middle Frontal Gyrus	L	6
-3	-38	9	32	-4,977	Posterior Cingulate	L	29
-50	-90	16	17	-4,664	Middle Occipital Gyrus	L	19
11	4	50	19	-4,551	Medial Frontal Gyrus	R	6
-28	34	11	46	-4,480	Inferior Frontal Gyrus	L	10
-65	-6	-3	21	-4,464	Middle Temporal Gyrus	L	21
-64	-21	1		-3,544	Superior Temporal Gyrus	L	22
28	9	51	11	-4,442	Middle Frontal Gyrus	R	6
-23	-67	67	11	-4,311	Superior Parietal Lobule	L	7
0	-15	10	11	-4,178	Thalamus (Medial Dorsal Nucleus)	L	/
-67	11	-11	16	-4,163	Superior Temporal Gyrus	L	38
-44	-15	48	40	-4,097	Precentral Gyrus	L	4
-32	-2	56	11	-3,961	Middle Frontal Gyrus	L	6
36	-45	49	12	-3,863	Inferior Parietal Lobule	R	40

-28	-30	62	24	-3,838	Postcentral Gyrus	L	3
-19	51	36	11	-3,811	Superior Frontal Gyrus	L	9
-59	-2	-25	7	-3,788	Middle Temporal Gyrus	L	21
-20	-10	69	10	-3,683	Superior Frontal Gyrus	L	6
-9	-60	51	21	-3,625	Precuneus	L	7
70	13	27	8	-3,498	Inferior Frontal Gyrus	R	9
-23	-78	56	9	-3,424	Precuneus	L	7
68	22	17	7	-3,405	Inferior Frontal Gyrus	R	45
-29	30	43	14	-3,339	Middle Frontal Gyrus	L	8
12	-76	41	9	-3,331	Precuneus	R	7
-31	-16	62	9	-3,308	Precentral Gyrus	L	6
-19	0	-1	7	-3,246	Lentiform Nucleus (Lateral Globus Pallidus)	L	/
-54	-56	52	8	-3,196	Inferior Parietal Lobule	L	40

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuroanatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described.

Supplementary Table 4: Activations to pain-related versus negative, neutral, and positive words in the comparison between CBP patients and HC.

x	y	z	Cluster size	t- value	Brain region		Brodmann area
30	-89	-26	83	4.849.770	Uvula, Pyramis	R	
-20	-96	-20	53	4.515.444	Fusiform Gyrus ,Tuber	L	18
-43	-53	61	10	4.474.019	Inferior Parietal Lobule	L	30
11	56	-4	10	4.334.582	Superior Frontal Gyrus	R	10
-48	22	4	28	4.327.287	Insula	L	/
-47	11	-6	12	4.163.378	Insula	L	/
43	19	14	17	4.148.976	Insula	R	/
21	37	-20	13	3.737.969	Inferior Frontal Gyrus	R	11
41	-55	63	12	3.568.240	Superior Parietal Lobule	R	7
-22	6	-30	14	-4.831.751	Uncus	L	28
48	21	-7	17	-4.418.987	Inferior Frontal Gyrus	R	47
-64	-66	15	10	-4.351.977	Middle Temporal Gyrus	L	39
-31	-14	62	13	-4.179.394	Precentral Gyrus	L	6
53	41	12	13	-4.127.489	Inferior Frontal Gyrus	R	46
-34	-43	4	10	-4.092.598	Caudate (Caudate Tail)	L	/
34	-19	43	10	-4.045.221	Postcentral Gyrus	R	3
-33	20	-22	15	-3.752.275	Superior Temporal Gyrus	L	38
-7	-79	27	15	-3.742.463	Cuneus	L	18
26	-14	66	20	-3.603.131	Precentral Gyrus	R	/
-32	-54	56	20	-3.501.765	Superior Parietal Lobule	L	7

Listed are clusters of activation with an uncorrected cluster threshold of $p < 0.01$. Talairach coordinates are provided for the maxima of the respective cluster. The corresponding neuroanatomical regions, the Brodmann areas, and the laterality (L, left; R, right) are described.

6 Literatur

Literatur

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Anhang A

Lebenslauf

Persönliche Daten	
Name:	Alexander Ritter
Geburtsdatum:	26.05.1980
Geburtsort:	Naumburg
Familienstand:	2 Kinder
11/07 – 05/14	Wissenschaftlicher Mitarbeiter am Lehrstuhl für Biologische und Klinische Psychologie an der Friedrich–Schiller–Universität Jena
04/04 – 09/07	Universität Leipzig: Psychologie, Diplom; Diplomarbeit „Development of an auditory n–back paradigm for attentional control in preattentive auditory processing“
10/02 – 03/04	TU Braunschweig: Psychologie, Vordiplom
09/99 – 07/00	Zivildienst an der Förderschule für geistig Behinderte Reichenbach
07/1999	Abitur am Christoph–Graupner–Gymnasium Kirchberg

Jena, 16. April 2014

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Alexander Ritter

Anhang B

Erklärung über den Eigenanteil

Erklärung über den Eigenanteil sowie über den Anteil weiterer Autoren an den veröffentlichten wissenschaftlichen Schriften, die in der Dissertationsschrift verwendet wurden, gemäß §7 Abs.3 Satz 3 der Promotionsordnung

1. Persönliche Angaben des Antragstellers

Ritter, Alexander

Institut:	Friedrich-Schiller-Universität Jena Institut für Psychologie LS für Biologische und Klinische Psychologie
Promotionsfach:	Psychologie
Thema der Dissertation:	Aspekte der Beeinflussung chronischen Rückenschmerzes durch zentralnervöse Prozesse

2. Nummerierte Aufstellung der eingereichten Schriften

1.Titel:	**Brain activity for visual judgment of lifted weight**
Autoren:	Ritter, A., Weiss, T., Franz, M., de Lussanet, M.
Zeitschrift:	Human Movement Science
Stand:	**veröffentlicht**
Volume:	32
Seiten:	924–937
Jahr:	2013
2.Titel:	**Human brain stem structures respond differentially to noxious heat**
Autoren:	Ritter, A., Franz, M., Dietrich, C., Miltner, W.H.R., Weiss, T.
Zeitschrift:	Frontiers in Human Neuroscience
Stand:	**veröffentlicht**
Volume:	7
Seiten:	1 - 10

Jahr: 2013

3.Titel: Enhanced Brain Responses to Pain-related Words in Chronic Back Pain Patients and its Relation to Current Pain

Autoren: Ritter, A., Franz, M., Grolla, A., Miltner, W.H.R., Weiss, T.

Stand: Eingereicht bei PAIN (am 15.9.2012), in Überarbeitung

3. Darlegung des Anteils aller Autoren sowie des Eigenanteils an diesen Schriften

zu Nr.1 - **Brain activity for visual judgment of lifted weight**

Konzeption (A.R. M.L., T.W.) Literaturrecherche (M.L., A.R.), Methodenentwicklung (A.R., M.L.), Versuchsdesign (A.R., M.L. T.W.), Datenerhebung (A.R.), Datenauswertung (A.R.), Ergebnisdiskussion (A.R., T.W. M.L.), Erstellen des Manuskriptes (A.R., M.L., T.W.)

zu Nr. 2 - **Human brain stem structures respond differentially to noxious heat**

Konzeption (A.R., T.W., C.D), Literaturrecherche (A.R., T.W. M.F., C.D.) Versuchsdesign (A.R., T.W., M.F.), Datenerhebung (A.R., M.F.), Datenauswertung (A.R., C.D., M.F.), Ergebnisdiskussion (T.W., A.R., C.D., M.F.), Erstellen des Manuskriptes (A.R., T.W., M.F., C.D., W.H.R.M.)

zu Nr.3 - **Enhanced Brain Responses to Pain-related Words in Chronic Back Pain Patients and its Relation to Current Pain**

Konzeption (T.W., A.R., A.G.), Literaturrecherche (A.R., T.W., M.F.) Methodenentwicklung (T.W., A.R.), Versuchsdesign (T.W., A.G.), Datenerhebung (A.G., A.R.), Datenauswertung (A.R., M.F.), Ergebnisdiskussion (A.R., T.W., M.F. W.H.R.M.), Erstellen des Manuskriptes (A.R., T.W., M.F., W.H.R.M.)

Bestätigung des Anteils der Mitautoren:

Ich bestätige die Richtigkeit der Angaben von Alexander Ritter bezüglich der Anteile:

Jena, 16. April 2014

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Thomas Weiss

Anhang C

Eigenständigkeitserklärung

Ich versichere, dass mir die geltende Promotionsordnung mit dem Stand vom April 2014 bekannt ist. Ich versichere, dass ich die Dissertationsschrift selbst angefertigt habe, dass ich keine Textabschnitte eines Dritten oder eigener Prüfungsarbeiten ohne Kennzeichnung übernommen habe und dass ich alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben habe.

Ich erkläre zudem, dass ich nicht die Hilfe eines Promotionsberaters in Anspruch genommen habe. Auch haben Dritte weder mittelbar noch unmittelbar geldwerte Leistungen von mir für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorliegenden Dissertation stehen.

Die Dissertation wurde nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht. Es wurde keine gleiche, eine in wesentlichen Teilen ähnliche oder andere Abhandlung bei einer anderen Hochschule bzw. anderen Fakultät als Dissertation eingereicht.

Jena, 16. April 2014

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Alexander Ritter